Information for Tables
In Ruth Institute Brochure:
Children and Donor Conception and Assisted Reproduction

(Please refer to the numbered reference list following these tables. The reference list also includes some commentary and explanations from me as well as definitions of some of the medical terms. Dr J)

Elevated Physical and Medical Risks Relevant to the Donor Conception and Assisted Reproduction Experience

Elevated Risks experienced by infants conceived through IVF or ICSI

Stillbirth 5,6	**Caesarean Section 5,6**
Pre-term Birth 5,6,18	**Low Birth Weight 6,7,18**
Cerebral palsy 6	**Rare genetic imprinting disorders, including Beckwith-Wiedemann Syndrome and Angelman Syndrome 14,23**
Major multiple birth defects 4,6	**Urogenital defects 6**
Musculoskeletal defects 4,6	**Asthma 10,11**
More frequent admission to the hospital 9,18	**Longer hospital stays 9**

Elevated Risks observed in children and adults conceived through IVF or ICSI

For all children	For girls only
Elevated or unusual distribution of body fat 16,21	**Discrepancy between bone-age and chronological age 22**
Higher fasting glucose levels 20	**Elevated levels of the hormones, LH and DHSEA 22**
Elevated blood pressure 20	**Binge drinking in adult women 19**
ADHD in adulthood 19	**Clinical depression in adult women 19**

Elevated Risks Associated with Low Birth Weight (Low birth weight and pre-term birth are risks of IVF)

Premature death in the first year 8	**neurosensory impairment 8**
Lower IQ 8	**Subnormal height 8**
Lower educational attainment 8	**Multiple chronic conditions 8**

Risks common to IVF and ICSI children:

1. Major multiple birth defects, 4, 6
2. musculoskeletal defects 4, 6
3. chromosomal defects 4
4. Stillbirth 5, 6
5. Caesarean section 5, 6
6. Pre-term birth 5, 6, 18
7. Urogenital defects 6
8. gastrointestinal defects 6
9. cerebral palsy 6
10. Lower birth weight, by almost one pound, than naturally conceived births 6, 7, 18
11. More frequently admitted to the hospital 9, 18
12. Longer hospital stays 9
13. Asthma 10, 11
14. Rare genetic imprinting disorders, including Beckwith-Wiedemann Syndrome, Angelman and possibly Silver Russell Syndrome 14, 23
15. Elevated or unusual distribution of body fat 16, 21
16. High blood pressure 20
17. Higher fasting glucose levels 20
18. Greater discrepancy between bone age and chronological age for girls 22
19. Elevated levels of hormones, including LH and DHEAS for girls 22
20. Binge drinking, adult women 19
21. ADHD, adult men and women 19
22. Clinical depression, adult women 19

Risks especially pronounced for children conceived through ICSI: ***(not listed on the brochure. Not found in all studies.)***

Autism 15
Mental retardation 15

Risks associated with low birth weight:
Premature death, within the first year 8
neurosensory impairment 8
subnormal height 8
lower IQ 8
Lower educational attainment 8
Multiple chronic conditions 8

Risks associated with advanced paternal age: (not listed on the brochure: running out of room!)
Austism 1
Bi-Polar Disorder 2
Schizophrenia 3

Research Relevant to Donor Conception and Assisted Reproduction

This reference list includes everything you need to find the original article. Statements in quotation marks are generally from the paper's Abstract. My additional commentary or explanations are generally in *italics. Dr J*

Advanced Paternal Age

(Although the Ruth Institute brochure did not explicitly address this topic, an "older" father, meaning a man over age 40, is often a factor in assisted reproduction situations. I include this information for the sake of completeness. Dr J)

1. "Advancing Paternal Age and Autism," **Archives of General Psychiatry** 2006;63(9); 1026-1032 (September 2006, Vol 63. No. 9) Abraham Reichenberg et al. http://www.ncbi.nlm.nih.gov/pubmed/16953005

A study of Jewish persons born in Israel who underwent draft board assessment at age 17. A subset, (n=132,271) had data on paternal and maternal age.

"There was a ***significant monotonic association between advancing paternal age and risk of Autism Spectrum Disorder (ASD).*** Offspring of men aged 40 years or older were 5.75 times more likely to have ASD than men younger than 30 years, after controlling for year of birth, socioeconomic status and maternal age. Advancing maternal age showed no association with ASD after adjusting for paternal age."

2. "Advancing Paternal Age and Bipolar Disorder," **Archives of General Psychiatry,** 2008;65(9)" 1034-1040, Emma M. Frans et al http://www.ncbi.nlm.nih.gov/pubmed/18762589

"After controlling for parity, maternal age, socioeconomic status and family history of psychotic disorders, there was ***a significant monotonic association between advancing paternal age and risk of Bipolar Disorder (BPD) in the offspring***. The offspring of men 55 years and older were 1.37 times more likely to be diagnosed with BPD than the offspring of men aged 20-24 years. The association with early onset BPD and advanced paternal age was even stronger: with offspring of fathers over age 50 2.81 times more likely to have a BPD diagnosis as offspring with fathers aged 20-24. Mother's age showed no significant impact, after adjusting for paternal age."

3. "Advancing Paternal Age and Schizophrenia," **Archives of General Psychiatry,** 2001;58(4)" 361-367 Dolores Malaspina et al

"After controlling for maternal age and other confounding factors (sex, ethnicity, education and duration of marriage) ***paternal age was found to be a strong and significant predictor of the schizophrenia diagnosis.*** Compared with offspring with fathers younger than 25 years, the relative risk of schizophrenia increased monotonically in each 5year age group, reaching 2.02 and 2.96 in offspring of men aged 45-49 and 50+ years respectively. Mother's age showed no significant impact, after adjusting for paternal age."

(This general story about advanced parental age may also interest readers: **http://www.nature.com/news/fathers-bequeath-more-mutations-as-they-age-1.11247 Dr J)**

Health Risks for Infants conceived through artificial techniques.

4. **"The risk of major birth defects after Intracytoplasmic sperm injection (ICSI) and In Vitro Fertilization, (IVF)"** Michle Hanse, Jennifer Kurinczuk, Carol Bower and Sandra Webb, The **New England Journal of Medicine,** May 7, 2002, Vol 346, no 10. 725-730. http://www.nejm.org/doi/pdf/10.1056/NEJMoa010035

"As compared with natural conception, the odds ratio for a major birth defect by one year of age, after adjustment for maternal age and parity, the sex of the infant and correlation between siblings, was 2.0 for ICSI and 2.0 for IVF. (In other words, the ART babies were twice as likely to have major birth defects than babies conceived naturally.) Infants conceived with use of assisted reproductive technology were more likely than naturally conceived infants to have **multiple major defects and to have chromosomal and musculoskeletal defects.** The risk remained significant when only singleton births were considered."
(Note: The term 'singleton births" is the technical term used to contrast with "multiple" births. This last statement means that the risk of multiple major defects associated with IVF cannot be explained away by the risks that arise due to the higher frequency of multiple births in IVF pregnancies. Dr J.)

5. J Perinatol. 2014 May;34(5):345-50. **Impact of ART on pregnancies in California: an analysis of maternity outcomes and insights into the added burden of neonatal intensive care.**

Merritt TA, Goldstein M, Philips R, Peverini R, Iwakoshi J, Rodriguez A, Oshiro B.

"Among ART/AI pregnancies, there was a 4-5fold increase in ***stillbirths*** compared to women whose pregnancy occurred naturally, while women with a history of infertility had a 2-3folr increase in the rate of stillbirths. ART/AI conceived pregnancies experienced a fourfold increase in the rate of ***cesarean section with associated complications and morbidities,*** over naturally conceived pregnancies. Mothers undergoing ART or AI had an almost 4-fold increase in the rate ***of preterm labor compared*** to those with natural conceptions. ***Multiple gestations*** increased 24-27fold among ART/AI conceptions compared to naturally conceived infants. A 2-3-fold increase

in ***known or suspected fetal anomalies among ART or AI*** compared to naturally conceived infants was observed."

6. **"Reproductive Technologies and the Risk of Birth Defects,"**

Michael J. Davies, et. al. **N Engl J Med** 2012; 366:1803-1813, May 10, 2012, http://www.nejm.org/doi/full/10.1056/NEJMoa1008095

"We observed associations of assisted conception with birth defects in analyses of ***single and multiple birth defects*** and in analyses that included or excluded cerebral palsy. Treatment with assisted reproductive technology was associated with ***increased risks of cardiovascular, musculoskeletal, urogenital, and gastrointestinal defects and cerebral palsy."***

(The risks between spontaneous and assisted conception do not appear significant for multiple births in this, and other studies. However, this is because the risks of birth defects are naturally elevated for multiple births. So, the difference between assisted and natural conception is swamped by the increased risks associated with any multiple birth. In these cases, we could say that the risks associated with assisted conception of a singleton looks more like the natural conception of multiples. Dr J)

This study also shows:
Lower birth weight for Assisted Reproduction, by almost a full pound. (6 # 8 oz. v 7 # 7 oz.) Higher likelihood of stillbirths, c-sections and pre-term birth.

5.6% of all assisted conception infants are born at less than 32 weeks gestation, compared with 1.1% of spontaneous conceptions. ➔ ART infants are 5 times more likely to be extremely premature.
19% of assisted conception infants are born between 32 and 36 weeks, compared with 5.5% of spontaneously conceived infants. ➔ ART infants are 3.5 times more likely to be moderately premature.

Add these two together to get total premature births:

25% of assisted conception infants are born at 36 weeks or less compared to 7% of spontaneous conceptions. 3.5 times more likely to be premature overall.

7. **"Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology,"**

Laura A. Schieve, Ph.D., Susan F. Meikle, M.D., Cynthia Ferre, M.S., Herbert B. Peterson, M.D., Gary Jeng, Ph.D., and Lynne S. Wilcox, M.D.
N Engl J Med 2002; 346:731-737March 7, 2002DOI: 10.1056/NEJMoa010806

http://www.nejm.org/doi/full/10.1056/NEJMoa010806

"As compared with all singleton infants born in the United States to women 20 years of age or older in 1997, singletons conceived with assisted reproductive technology in 1996 or 1997 were at ***increased risk for low and very low birth weight.***

We estimate that more than 3 percent of the low-birth-weight infants and more than 4 percent of the very-low-birth-weight infants born in 1997 were conceived with assisted reproductive technology — six times the proportions that would be expected on the basis of the frequency of these procedures. These higher-than-expected proportions are largely explained by the increased rate of multiple births."

8. "Outcomes in Young Adulthood for Very-Low-Birth-Weight Infants," Maureen Hack, et. al. **N Engl J Med** 2002; 346:149-157 January 17, 2002 http://www.nejm.org/doi/full/10.1056/NEJMoa010856#t=article

This study describes the risks associated with Very Low Birth Weight. Since this is a significant risk factor associated with Assisted Reproduction, I thought it prudent to include this here and on the brochure. These paragraphs are my summary of the procedures and sample used. I highlighted a few particularly noteworthy items:

> A 20 year follow up study of 242 20 year olds who had been very low birth weight (ie an average weight of 1179 g and a mean gestational age of 29.7 weeks.)
>
> To show the risks of very-low-birth weight: the study describes its original sample this way: "A cohort of 490 very-low-birth-weight infants were admitted to Rainbow Babies and Children's Hospital in Cleveland between 1977 and 1979. A total of 316 children (64 percent) survived to their second year. *(In other words, 174 died in their first year.) Dr J* One child died of a brain tumor between 2 and 8 years of age, and three died between 8 and 20 years of age — one from meningitis, one by drowning, and one from sequelae of severe spastic quadriplegia. Of the remaining 312 subjects, 70 were not studied: 58 could not be located, 5 lived out of state, 6 declined to participate, and 1 with severe spastic quadriplegia could not be interviewed."

These paragraphs are direct quotes from the study:

> Very-low-birth-weight participants had significantly higher rates of chronic conditions than the controls (33 percent vs. 21 percent, P=0.002). The difference was primarily attributable to ***higher rates of neurosensory impairment and subnormal height.*** Chronic Conditions at 20 Years of Age among Very-Low-Birth-Weight and Normal-Birth-Weight Participants.). A total of 23 percent of the very-low-birth-weight participants had one chronic condition, 9 percent had two chronic conditions, and 1 percent had three or more chronic conditions. In comparison, 17 percent of the controls had one chronic condition, and 4 percent had two chronic conditions (P=0.005).

Fewer very-low-birth-weight participants than normal-birth-weight participants had ***graduated from high school or obtained a general equivalency diploma*** by 20 years of age (74 percent vs. 83 percent, P=0.04) Level of Education at 20 Years of Age among Very-Low-Birth-Weight and Normal-Birth-Weight Participants.). Forty percent of the very-low-birth-weight participants had ***repeated a grade in school***, as compared with 27 percent of the normal-birth-weight participants (P=0.003). Very-low-birth-weight participants who graduated from high school did so at a mean age of 18.2±0.6 years, as compared with 17.9±0.6 years among the controls (P<0.001). Fewer very-low-birth-weight men were enrolled in postsecondary studies, of whom only 16 percent were in a four-year college program, as compared with 44 percent in the control group (P<0.001).
The differences in grade repetition, educational attainment, and current enrollment in educational programs remained significant when the comparisons were restricted to participants without neurosensory impairment or subnormal IQ (<70).

Very-low-birth-weight participants had ***significantly lower mean IQ scores*** than the controls (87 vs. 92, P<0.001) and had lower scores on the subtests of academic achievement. They also had a higher frequency of subnormal IQ (<70) and borderline IQ (70 to 84). Fifty-one percent of the very-low-birth-weight participants had an IQ in the normal range (≥85), as compared with 67 percent of the controls (P<0.001). These differences remained significant when the comparisons were restricted to the participants without neurosensory impairment.

9. **Post-neonatal hospitalization and health care costs**

"Post-neonatal hospitalization and health care costs among IVF children: a 7-year follow-up study," Sari Koivurova, et. al. **Human Reproduction** pp. 1–6, 2007
http://humrep.oxfordjournals.org/content/early/2007/06/21/humrep.dem150

"The full-sample and singleton analyses showed that IVF children were significantly more ***frequently admitted to hospital*** (mean 1.76 vs. 1.07, P < 0.0001; 1.61 vs. 1.07, P 5 0.0004, respectively) and spent ***significantly more days in the hospital*** (mean 4.31 vs. 2.61, P < 0.0001; 3.47 vs. 2.56, P 5 0.0014, respectively) than control children. No differences were detected between IVF and control twins. The costs of post-neonatal hospital care per child were 2.6-fold for IVF singletons, but 0.7-fold for IVF twins when compared with controls. Cost estimation showed 2.6-fold costs for total IVF population in comparison to general population based controls."

10. Asthma in children born after infertility treatment: findings from the UK Millennium Cohort Study C. Carson, et. al. **Human Reproduction**, Vol.28, No.2 pp. 471–479, 2013

http://humrep.oxfordjournals.org/content/28/2/471.full.pdf+html

"main results and the role of chance: Compared with planned children, those born to subfertile parents were significantly more likely to ***experience asthma,*** wheezing and to

be taking anti-asthmatics at 5 years of age [adjusted odds ratio (OR): 1.39 (95% confidence interval (CI): 1.07, 1.80), OR: 1.27 (1.00, 1.63) and OR: 1.90 (1.32,2.74), respectively]. This association was mainly related to an increase among children born after ART (adjusted OR: 2.65 (1.48, 4.76), OR: 1.97, (1.10, 3.53) and OR: 4.67 (2.20, 9.94) for asthma, wheezing and taking anti-asthmatics, respectively). The association was also present, though reduced, at the age of 7 years.
limitations, reasons for caution: The number of singletons born after ART was relatively small (n ¼ 104), and as such the findings should be interpreted with caution. However, data on a wide range of possible confounding and mediating factors were available and analysed. The data were weighted for non-response to minimize selection bias.
wider implications of the findings: The findings add to the growing body of evidence suggesting an association between subfertility, ART and asthma in children. Further work is needed to establish causality and elucidate the underlying mechanism. These findings are generalizable to singletons only, and further work on multiples is needed."

11. Asthma in Swedish children conceived by in vitro fertilization,

Bengt Källén, Orvar Finnström, Karl-Gösta Nygren Petra Otterblad Olausson *Archives of Disease in Childhood* 2013;**98**:92-96
http://adc.bmj.com/content/98/2/92.abstract

"A significantly increased risk for asthma, albeit small, was found in children conceived by IVF (aOR 1.28, 95% CI 1.23 to 1.34), increasing the absolute risk from 4.4% to 5.6%. The risk increase for asthma was the same in boys and girls, in singletons and twins, and after caesarean section and vaginal delivery. The risk was higher for preterm than term singletons. For children with a low Apgar score, respiratory diagnoses, mechanical ventilation, continuous positive airway pressure or neonatal sepsis, the effect of IVF on asthma risk was low and statistically non-significant. Adjustment for length of involuntary childlessness eliminated the effect, and removal of infants whose mothers had used antiasthmatics in early pregnancy reduced the risk.
Conclusions This study verifies an association between IVF and asthma in children. This can be partly explained by neonatal morbidity and by maternal asthma acting as mediators, but the main risk factor is parental subfertility. The mechanism for this is unclear."

12. The longer-term health outcomes for children born as a result of IVF treatment: Part I–General health outcomes

Roger Hart, and Robert J. Norman
Human Reproduction Update, Vol.19, No.3 pp. 232–243, 2013
http://humupd.oxfordjournals.org/content/19/3/232.full.pdf+html

"RESULTS Limited long-term follow-up data suggest that there is potentially an increase in the incidence of ***raised blood pressure, elevated fasting glucose, increase in total body fat composition, advancement of bone age and potentially subclinical thyroid disorder in the IVF offspring.*** Whether these potential associations are related to the IVF

treatment *per se*, the adverse obstetric outcomes associated with IVF treatment or are related to the genetic origin of the children is yet to be determined.
CONCLUSIONS This review provides evidence to suggest that the short-term health outcome for children born from IVF treatment is positive. However, it is expected that the cardiovascular and metabolic risk factors found in childhood and tracking into adulthood could be worse in later life, and may be responsible for chronic cardiometabolic disease. These observations need to be addressed by further studies.

Conflict of interest R.H. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins. R.J.N. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins."

13. "The longer-term health outcomes for children born as a result of IVF treatment. Part II –Mental health and development outcomes," Roger Hart and Robert J. Norman

Human Reproduction Update, Vol.19, No.3 pp. 244–250, 2013
http://humupd.oxfordjournals.org/content/19/3/244.full.pdf+html

"From the Abstract: results: Limited long-term follow-up data suggest that there is an ***increase in the incidence of cerebral palsy and neurodevelopmental delay related to the confounders of prematurity and low birthweight***. Previous reports of associations with autism and attention-deficit disorder are believed to be related to maternal and obstetric factors. ***There exists a potential increase in the prevalence of early adulthood clinical depression and binge drinking in the offspring of IVF***, with the reassuring data of no changes with respect to cognitive development, school performance, social functioning and behaviour. Whether these potential associations are related to the IVF treatment, the adverse obstetric outcomes associated with IVF treatment, the genetic or subsequent environmental influences on the children is yet to be determined. **Conclusions**: In general, the longer-term mental and emotional health outcome for children born from IVF treatment is reassuring, and is very similar to that of naturally conceived children; however, further studies are required to explore any association with depression, and its causality in more detail.

Conflict of interest R.H. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins. R.J.N. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins."

Rare Genetic Disorders

14. Characterization of DNA methylation errors in patients with imprinting disorders conceived by assisted reproduction technologies Hitoshi Hiura, et. al.

Human Reproduction, Vol.27, No.8 pp. 2541–2548, 2012 Advanced Access publication on June 6, 2012 doi:10.1093/humrep/des197
http://humrep.oxfordjournals.org/content/27/8/2541.full.pdf+html

results: We found a 10-fold increased frequency of BWS and SRS associated with ART. The majority of ART cases showed aberrant DNA methylation patterns at multiple imprinted loci both maternal and paternal gDMRs (5/6), with both hyper- and hypomethylation events (5/6) and also mosaic methylation errors (5/6). Although our study may have been limited by a small sample number, the fact that many of the changes were mosaic suggested that they occurred after fertilization. In contrast, few of the patients who were conceived naturally exhibited a similar pattern of mosaic alterations. The differences in methylation patterns between the patients who were conceived naturally or after ART did not manifest due to the differences in the disease phenotypes in these imprinting disorders.
conclusion: A possible association between ART and BWS/SRS was found, and we observed a more widespread disruption of genomic imprints after ART. The increased frequency of imprinting disorders after ART is perhaps not surprising given the major epigenetic events that take place during early development at a time when the epigenome is most vulnerable.

BWS= Beckwith-Wiedemann Syndrome or
https://en.wikipedia.org/wiki/Beckwith%E2%80%93Wiedemann_syndrome
SRS= Silver Russell Syndrome or
https://en.wikipedia.org/wiki/Silver%E2%80%93Russell_syndrome

15. "Autism and Mental Retardation Among Offspring Born After In Vitro Fertilization," Sven Sandin, et. al.

JAMA. 2013;310(1):75-84.
http://jama.jamanetwork.com/article.aspx?articleid=1707721#Abstract

"Conclusions and Relevance: Compared with spontaneous conception, IVF treatment overall was not associated with autistic disorder but was associated with a small but statistically significantly increased risk of mental retardation. For specific procedures, IVF with ICSI for paternal infertility was associated with a small increase in the RR for autistic disorder and mental retardation compared with IVF without ICSI. The prevalence of these disorders was low, and the increase in absolute risk associated with IVF was small."

16. "Are ICSI adolescents at risk for increased adiposity?" **Human Reproduction**, Vol.27, No.1 pp. 257–264, 2012

Florence Belva, et. al. http://humrep.oxfordjournals.org/content/27/1/257.full.pdf+html

"Conclusion: We found that pubertal ICSI girls were more prone to central, peripheral and total adiposity compared with their SC counterparts. ICSI adolescents with advanced pubertal stages showed more peripheral adiposity."

17. "Growth during infancy and early childhood in relation to blood pressure and body fat measures at age 8–18 years of IVF children and spontaneously conceived controls born to subfertile parents," Manon Ceelen et. al. 1 **Human Reproduction,** Vol.24, No.11 pp. 2788–2795, 2009 http://humrep.oxfordjournals.org/content/24/11/2788.full.pdf+html

18. "In vitro fertilization and preterm delivery, low birth weight, and admission to the neonatal intensive care unit: a prospective follow-up study," Kirsten Wisborg, Hans Jacob Ingerslev, Tine Brink Henriksen, **Fertility and Sterility**, November 2010 Volume 94, Issue 6, Pages 2102–2106,

http://www.fertstert.org/article/S0015-0282(10)00074-9/fulltext

"After adjustment we found a statistically significantly increased risk of preterm delivery and very preterm delivery in women who conceived after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) compared with fertile women. Compared with fertile women, the risk of preterm delivery and very preterm delivery was not statistically significantly different in women pregnant after non-IVF assisted reproductive treatment (non-IVF ART) or subfertile women. We found no association between IVF/ICSI and the risk of low birth weight at term or admittance to the NICU."

19. "A cross-sectional evaluation of the first cohort of young adults conceived by in vitro fertilization in the United States," Hind A. Beydoun, et. al. **Fertility and Sterility**, November 2010, Vol 94, Issue 6, pp. 2043-2049

http://www.fertstert.org/article/S0015-0282(09)04209-5/fulltext

"A total of 173 (31%) of 560 eligible young adults completed the questionnaire. Mean age was 21.2 years (range 18–26 years) and male-to-female ratio was 3:4. A limited number were conceived through gamete donation but none through oocyte/embryo micromanipulation. Prevalence rates of overweight and obesity were 35% and 10%, respectively. More than 65% were ever diagnosed with a chronic condition; most diagnoses were psychiatric, ocular, respiratory, and cardiometabolic in nature. Almost 40% of respondents were lifetime smokers, 62% reported binge drinking in the previous year, and >90% were physically active in the preceding month. Survey participants were mostly similar to a subsample of the 1999–2004 National Health and Nutrition Examination Survey on selected health indicators."

20. "Cardiometabolic Differences in Children Born After in Vitro Fertilization: Follow-Up Study," Manon Ceelen, et. al. **J Clin Endocrinol Metab**, May 2008, 93(5):1682–1688 http://press.endocrine.org/doi/pdf/10.1210/jc.2007-2432

"Results: Systolic and diastolic blood pressure levels were higher in IVF children than controls. Children born after IVF were also more likely to be in the highest systolic and diastolic blood pressure quartiles (odds ratio 2.1, 95% confidence interval 1.4, 3.3; odds ratio 1.9, 95% confidence interval 1.2, 3.0, respectively). Furthermore, higher fasting glucose levels were observed in pubertal IVF children (5.0 0.4 vs. 4.8 0.4 mmol/liter in controls; P 0.005). Blood pressure and fasting glucose differences could not be explained by current body size, birth weight, and other early life factors or by parental characteristics, including subfertility cause."

21. "Body Composition in Children and Adolescents Born after in Vitro Fertilization or Spontaneous Conception," Manon Ceelen, et. al. **J Clin Endocrinol Metab, 2007,** 92(9):3417–3423, **http://press.endocrine.org/doi/pdf/10.1210/jc.2006-2896**

"Results: IVF children had a significantly lower subscapular-triceps skinfold ratio and a significantly higher sum of peripheral skinfolds, peripheral body mass, and percentage of peripheral body fat as compared with controls. Although not reaching statistical significance, both dual-energy x-ray absorptiometry and skinfold measurements suggested that total body fat in IVF children is increased. Neither current and early risk factors nor parental factors, such as subfertility cause, could explain the differences in peripheral fat assessed by anthropometry between IVF children and controls. No differences in bone mineral composition between IVF children and controls were found. **Conclusions:** Our observations indicate that body fat composition in IVF children is disturbed. Follow-up of IVF children to monitor body fat pattern and potentially related health problems from adolescence into adulthood is of great importance."

22. "Pubertal development in children and adolescents born after IVF and spontaneous conception," Manon Ceelen et.al. **Human Reproduction** Vol.23, No.12 pp. 2791–2798, 2008, http://humrep.oxfordjournals.org/content/23/12/2791.full.pdf+html

"RESULTS: Pubertal stage and age at menarche were not significantly different between IVF and control children. In the pubertal subpopulation, a higher bone age–chronological age (BA–CA) ratio and a larger BA–CA difference were observed in IVF-conceived girls compared with. Furthermore, dehydroepiandrosterone sulphate (DHEAS) and LH levels were significantly higher in IVF-conceived girls than in control subjects. **CONCLUSIONS:** Bone age appeared to be advanced in pubertal IVF-conceived girls, but not in boys, compared with controls. Increased DHEAS and LH concentrations were found among IVF girls."

23. "A review of known imprinting syndromes and their association with assisted reproduction technologies," David J. Amor and Jane Halliday, **Human**

Reproduction Vol.23, No.12 pp. 2826–2834, 2008
http://humrep.oxfordjournals.org/content/23/12/2826.full.pdf+html

"An association between assisted reproduction technologies (ART) and abnormal genomic imprinting in humans has been recognized for several years; however, the magnitude of this risk and the spectrum of imprinting syndromes to which the risk applies remains unknown. Nine human imprinting syndromes have been identified but current evidence links ART with only three: Beckwith–Wiedemann syndrome, Angelman syndrome and the newly described maternal hypomethylation syndrome. There is currently a lack of evidence linking ART with the remaining six imprinting syndromes: Prader–Willi syndrome, Russell–Silver syndrome, maternal and paternal uniparental disomy of chromosome 14, pseudohypoparathyroidism type 1b and transient neonatal diabetes. Evidence from clinical reports suggests that the association between imprinting syndromes and ART may be restricted to syndromes where the imprinting change takes the form of hypomethylation on the maternal allele. In contrast, studies of gametes and early embryos suggest that ART can be associated with hypermethylation as well as hypomethylation, with imprinting changes occurring on paternal as well as maternal alleles. The health effects of ART-associated imprinting changes may also extend beyond the nine recognized imprinting syndromes."

24. **"My Daddy's Name is Donor:" A New Study of Young Adults Conceived Through Sperm Donation,** Elizabeth Marquardt, Norval D. Glenn and Karen Clark, (New York, New York: Institute for American Values, 2010).

(In addition to the quotations on the brochure from the Anonymous Us website, readers may also be interested in these findings. Dr. J)

Donor Conceived Persons are more likely to say:

- "It bothers me that money was exchanged in order to conceive me."
- "My sperm donor is half of who I am."
- "The circumstances of my conception bother me."
- "I have worried that if I try to get more information about or have a relationship with my sperm donor, my mother and/or the father who raised me would feel angry or hurt."
- "I find myself wondering what my sperm donor's family is like."
- "I sometimes wonder if my sperm donor's parents would want to know me."
- "When I see friends with their biological fathers and mothers, it makes me feel sad."
- "It hurts when I hear other people talk about their genealogical background."
- "I feel confused about who is a member of my family and who is not."
- "I worry that my mother or father might have lied to me about important matters when I was growing up."
- "When I see someone who resembles me I often wonder if we are related."
- "When I'm romantically attracted to someone I have worried that we could be unknowingly related."

Definitions:

Third Party Reproduction may utilize IVF, ICSI or Intrauterine Insemination. (IUI) In the IUI procedure, the sperm is inserted directly into the uterus, using a catheter. IUI does not involve fertilizing the egg outside of the body.

IUI:
A semen sample will be washed by the lab to separate the semen from the seminal fluid. A catheter will then be used to insert the sperm directly into the uterus. This process maximizes the number of sperm cells that are placed in the uterus, thus increasing the possibility of conception.

http://americanpregnancy.org/infertility/intrauterine-insemination/

IVF:
IVF is the process of fertilization by manually combining an egg and sperm in a laboratory dish, and then transferring the embryo to the uterus.

http://americanpregnancy.org/infertility/in-vitro-fertilization/

ICSI:
Intracytoplasmic sperm injection (ICSI) involves the direct injection of sperm into eggs obtained from in vitro fertilization (IVF).

http://americanpregnancy.org/infertility/intracytoplasmic-sperm-injection/

GIFT:
GIFT is an assisted reproductive procedure which involves removing a woman's eggs, mixing them with sperm, and immediately placing them into a fallopian tube.
One of the main differences between this procedure andin vitro fertilization (IVF) and zygote intrafallopian transfer (ZIFT) procedures is that with GIFT the fertilization process takes place inside the fallopian tube rather than in a laboratory. However, healthy tubes are necessary for GIFT to work.

http://americanpregnancy.org/infertility/gamete-intrafallopian-transfer/

ZIFT:
ZIFT is an assisted reproductive procedure similar to in vitro fertilization and embryo transfer, the difference being that the fertilized embryo is transferred into the fallopian tube instead of the uterus.
The main difference between ZIFT and GIFT is that ZIFT transfers a fertilized egg directly into the fallopian tubes while GIFT utilizes a mixture of sperm and eggs.

http://americanpregnancy.org/infertility/zygote-intrafallopian-transfer/

Adiposity: https://en.wikipedia.org/wiki/Body_adiposity_index
The **body adiposity index** (**BAI**) is a method of measuring the amount of body fat in humans. The BAI is calculated without using body weight, unlike the body mass index (BMI). Instead, it uses the size of the hips compared to the person's height. Based on population studies, the BAI is approximately equal to the percentage of body fat for adult men and women of differing ethnicities.[1]
http://www.bariatric-solutions.com/wDeutsch/for-patients/adiposity/definition-and-diagnosis.php?navid=13

Bone Age- Chronological Age: **Bone age** is the degree of maturation of a child's bones. As a person grows from fetal life through childhood,puberty, and finishes growth as a young adult, the bones of the skeleton change in size and shape. These changes can be seen by x-ray. The "bone age" of a child is the average age at which children reach this stage of bone maturation. A child's current height and bone age can be used to predict adult height. For most people, their bone age is the same as their biological age but for some individuals, their bone age is a couple years older or younger. Those with advanced bone ages typically hit a growth spurt early on but stop growing early sooner while those with delayed bone ages hit their growth spurt later than normal. Kids who are below average height do not necessarily have a delayed bone age; in fact their bone age could actually be advanced which if left untreated, will stunt their growth.

https://en.wikipedia.org/wiki/Bone_age

DHEAS: **Formal name:** Dehydroepiandrosterone Sulfate
DHEAS levels are not routinely measured. A DHEAS test may be ordered, along with other hormone tests, whenever excess (or, more rarely, deficient) androgen production is suspected and/or when a health practitioner wants to evaluate a person's adrenal gland function.
It may be measured when a woman presents with signs and symptoms such as amenorrhea, infertility, and/or those related to virilization. These changes vary in severity and may include:

- A deeper voice
- Excess facial or body hair (hirsutism)
- Male pattern baldness
- Muscularity
- Acne
- Enlargement of the Adam's apple
- Decreased breast size

It may also be ordered when a young girl shows signs of virilization or when a female infant has external genitalia that are not distinctly male or female in appearance (ambiguous genitalia).
DHEAS may also be measured when young boys show signs of precocious puberty, the development of a deeper voice, pubic hair, muscularity, and an enlarged penis well before the age of normal puberty.
https://labtestsonline.org/understanding/analytes/dheas/tab/test/

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