HHS Public Access

Author manuscript

Semin Reprod Med. Author manuscript; available in PMC 2020 March 13.

Published in final edited form as:

Semin Reprod Med. 2018 May ; 36(3-04): 204–210. doi:10.1055/s-0038-1677526.

Transitioning from infertility-based (ART 1.0) to elective (ART 2.0) use of assisted reproductive technologies and the DOHaD hypothesis: do we need to change consenting?

Paolo Rinaudo, **Amanda Adeleye**

Division or Reproductive Endocrinology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, San Francisco, California.

Abstract

The use of assisted reproductive technologies (ART) has increased significantly in recent years. While this is partially due to improved access for infertile patients, another contribution to the growth of ART utilization is represented by individuals without infertility, who electively chose to freeze their gametes and embryos for future use, before ever attempting conception spontaneously.

Overall, the safety of ART for parents and children is well described and the risks are modest. However, while long-term health consequences for offspring as postulated by the Developmental Origin of Health and Disease (DOHaD) hypothesis are unknown, numerous animal studies suggest a predisposition for chronic diseases like hypertension and glucose intolerance.

In this article, we argue that a key difference exists between infertile patients, who need to use ART as the only means to achieve pregnancy, and (likely) fertile patients who elect to use ART techniques as a family planning option. We believe that the two sets of patients are different and their risks benefit ratios are different. We propose that while all patients should be aware of the risks, patients planning to utilize ART techniques without a diagnosis of infertility should be encouraged to think critically about the additional risks, particularly the "potential" long-term risks that may be imposed from these elective procedures.

Assisted reproductive technologies are increasingly used

The use of ART has increased exponentially since the birth of Louise Brown in 1978, the first child conceived from IVF. As a striking example, while in the first 4 years since Brown's birth, only 4 children were born following the use of ART[1,2], it is estimated that almost 8 million children have been conceived with ART since then.[3] Further, it is expected that 2.4 million procedures will be performed in the coming years and over 500,000 children will be born annually from ART.[4,3] These numbers are anticipated to grow over the next several decades and it is expected that approximately 1 to 3% of the world population will be conceived with ART by the year 2100.[5]

In recent years, there has been a change in the utilization of ART. While in the past (what could be called: "**ART 1.0**") the diagnosis of infertility was indispensable to start treatment, currently, an increasing number of individuals without a formal diagnosis of infertility are choosing to utilize ART as a form of family planning ("**ART 2.0**"). In addition, there is a much faster transition to utilize ART after fewer ovulation induction cycles. In fact, the

FASTT trial has shown that compared with conventional infertility treatment and when the woman is younger than 40 years, an accelerated approach to IVF that starts with clomiphene and intrauterine insemination (IUI), but eliminates cycles with gonadotropin and IUI, results in a shorter time to pregnancy with fewer treatment cycles, and at a lower cost.[6]

Individuals who electively plan to use ART are represented in large part by women planning to freeze their eggs or couples who want to generate embryos for future use.

Egg freezing is an outstanding opportunity to preserve fertility and it is a welcomed additional service to patients.[7] Since 2013, oocyte cryopreservation is no longer considered experimental by the American Society of Reproductive Medicine.[8] As opposed to medically indicated oocyte cryopreservation, also referred to as fertility preservation, social cryopreservation seeks to address anticipated age-related infertility. Women are increasingly using cryopreserved oocytes and a greater number have stated intentions to use such oocytes in the future.[9]

It is surprisingly challenging to estimate the number of women who are currently freezing oocytes. In 2016, according to SART data, there were 8825 completed oocyte cryopreservation cycles in the United States (an eleven-fold increase since 2009), a number that is expected to greatly increase in the future. [10] For women that ultimately decide to use their oocytes when their fertility has been impacted, social oocyte cryopreservation is an important and effective family building solution.

Another group of patients using ART electively are those who decide to freeze their embryos without a history of infertility. This group of patients is distinct from individuals who utilize embryo cryopreservation as a necessary procedure to freeze supernumerary embryos. Patients performing elective embryo banking may do so because they are aware of the decline of fertility with age and they might have competing professional or personal needs.[11] Some couples do so because they have advanced maternal age and would like to have more than one child. They might decide to freeze embryos for future use, and then attempt natural conception for the “first” child.

Data collection around the intention of oocyte or embryo cryopreservation is limited. It is therefore difficult to estimate the number of people pursing elective embryo or oocyte cryopreservation. While almost a quarter of ART cycles in the United States are for embryo banking, the majority of these cycles are represented by supernumerary embryos or embryos frozen following preimplantation genetic screening.[12]

1. Safety of assisted reproductive technologies

Although all medical interventions have some associated adverse effects, it is appropriately assumed that ART technologies are safe (for a review see Feuer and Rinaudo, 2013).[13] Further, for patients carrying a Mendelian disease, conception with ART maybe safer than coital conception.

Overall, while short term risks, including obstetrical and neonatal risks have been well described, there is a paucity of data that asses the long-term health of ART children or children conceived with non-IVF fertility treatment.[14,15]

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, embryonic and fetal exposures to non-physiologic conditions (undernutrition or over nutrition, presence of toxicants or even embryo culture in vitro) during this sensitive time of development can impact the long-term health of offspring.[16] The organism adapts to the abnormal conditions encountered during development with the net result that survival is possible, but with predisposition to chronic diseases like hypertension, cardiovascular disease or glucose intolerance. Epigenetic changes are the biologic mechanism that most likely explains this phenomenon. In fact, it is well known that the preimplantation period is a time of profound changes in DNA methylation and histone marks.[17,18] Embryo culture in vitro has been associated with alterations in the expression of imprinted genes and an increase in imprinting disorders amongst ART children.[19,20]

Animal studies have begun to shed light on the biological plausibility of this hypothesis and have confirmed the presence of abnormalities in placental and fetal growth. In a study by Bloise et al., mice conceived from IVF had larger placentas with less efficient nutrient transport compared to spontaneously-conceived blastocysts. Furthermore, IVF concepti were smaller than their spontaneously conceived counterparts during early gestation, while starting at mid-gestation they showed increased fetal and placental growth with the net result that normal weight was achieved at term[21]. Abnormalities in fetal and neonatal growth have also been demonstrated in cattle and sheep conceived from IVF as well.[22,23]

Importantly, animal studies are particularly useful to analyze the postnatal phenotype (see Duranthon, 2018 for an excellent review).[22] Given their shorter lifespan, animals offer the possibility of assessing the long-term health effects of ART procedures in a reasonable amount of time. In classic studies, alterations in anxiety levels and memory were observed in adult mice conceived by IVF or cultured during the preimplantation period.[24,25] More importantly, numerous studies have demonstrated evidence of altered metabolism in adult mice as well. Embryo culture was found to be associated with an increased systolic blood pressure in mice in several but not all studies.[26,27, 21] Our laboratory has found that IVF in mice is associated with alterations in offspring growth and glucose homeostasis in adulthood.[28,29] While there is no evidence that ART affects longevity in mice, it has been shown that the combined exposure of IVF *and* a high fat diet results in a 30% decline in their lifespan.[27,30]

In humans, studies have confirmed poorer obstetric and neonatal outcomes amongst pregnancies conceived with ART compared to spontaneously conceived offspring. [31,14,15] Human data on the long-term outcomes of ART offspring are limited given the young age of the majority of ART children [32]. However, there are emerging data to suggest that glucose tolerance and the potential for cardiovascular disease are altered in children conceived with ART. A recently published meta-analysis including ten studies showed a small but statistically significant increase in blood pressure of ART offspring compared to naturally conceived children.[33] More concerning, in a small study, Meister et al. demonstrated a six-fold increase in the diagnosis of hypertension in ART conceived children compared to age matched controls.[34] The University of Groningen (Netherlands) is currently following 194 children conceived from sub-fertile couples by either spontaneous conception, mini-IVF or conventional IVF. They have demonstrated that systolic blood pressures are significantly

higher in children conceived from conventional IVF compared to mini- IVF at age 4.[35] However, a further follow up in the same cohort of children at age 9 found no differences in blood pressure between the groups.[36] Belva et al. suggested that IVF children have a lower ability to respond to stressful conditions and if a second stressor is added, hypertension would occur. As an example of this possibility, Scherrer et al. demonstrated that IVF/ICSI-children exposed to high-altitude had evidence of pulmonary hypertension and diastolic dysfunction while normally conceived children did not.[37] Similarly, Chen et al. showed that IVF offspring exposed to three days of overfeeding displayed higher systolic blood pressure compared to controls.[38] Regarding alterations in glucose tolerance, several authors have found evidence of insulin resistance in ART children compared to spontaneously conceived control[32],[39]. It was also shown that ART children display mild evidence of altered glucose tolerance when exposed to overfeeding.[38]

Some important caveats need to be discussed when analyzing the long-term health data in animals and humans.[40,41] First, some investigators argue that animal data and models cannot be appropriately extrapolated to assess the impact of ART in humans.[40,41] For instance, there are significant differences in implantation and trophoblast invasion in the murine placenta compared to humans.[42] It is possible that some of the demonstrated altered effects of growth and development in mice conceived by ART may be attributed to the differences in how the early murine embryo is established and implants compared to humans embryos.

Second, several obstacles limit adequate assessments of human studies on the impact of ART. Examples of such scientific challenges include the ethical limitations of performing high quality studies (such as randomized clinical trials) in which the outcome in question may negatively impact a child's health; the heterogeneity in ART interventions and the patients receiving them; the rapidly evolving nature of the technology; and finally the significant resource expenditure required to perform such studies.[43,44]

Taken together, evidence from animal models and the limited human data indicate that the preimplantation period is a time of reprogramming and therefore ART offspring could be potentially more vulnerable to a "second hit" (like unhealthy diets or lack of exercise) and at higher risk to develop chronic diseases when adults.

2. The more procedures, the more risks?

Several ART procedures are required to achieve successful conception. For women who initially presented for oocyte cryopreservation, at a minimum, six procedures need to be completed to achieve pregnancy in the future.

1. Superovulation
2. Oocyte retrieval
3. Oocyte freezing
4. Oocyte thawing
5. ICSI
6. Culture of embryo(s) for 2–3 days with transfer

However, a patient could choose four additional procedures:

7. Extended culture, to the blastocyst state
8. Embryo biopsy with preimplantation genetic testing
9. Embryo freezing
10. Embryo thawing and transfer (if a euploid embryo is present).

The choice between the "basic" or the "expanded" option is the result of a shared decision between the physician and the patient/ couple. The choice is complex, since evidence-based data are often missing and different physicians may hold varying opinions. For example, currently there is a very active debate on the use and safety of preimplantation genetic testing (PGT),[45] with some groups supporting the technique and others opposing it.[46] It is clear that many patients feel strongly about the need of PGT and often request it [47]

Particularly relevant to this discussion is that murine models have consistently shown that there is a relationship between the invasiveness of ART and the relative impact on offspring. For example, culturing embryos in progressively suboptimal conditions will result in an increasingly altered gene expression profiles (Figure 1). Importantly, there is an association between gene expression changes in the blastocysts and altered glucose tolerance in the adult (Figure 2). Similarly, steroid clearance is increased in the placentas of ICSI concepti compared to conventional IVF concepti.[48] From an epigenetic point of view, the Bartolomei group has shown that placental and imprinted gene alterations increase when more procedures are performed, with a dose response effect. In particular, there is a progressive worsening of placental and epigenetic alterations from murine fetuses exposed to embryo transfer alone (low level of intervention), to superovulation + embryo transfer (intermediate), to superovulation + IVF + embryo transfer (high level of ART intervention).[49]

3. Should Patients using ART without a diagnosis of infertility be informed of the potential long-term health effects in offspring?

The guidelines for consenting patients for ART procedures are limited with much of the focus on the legal implications of parenthood.[50] Informed consent guidelines recommend that prior to consent signing, relevant information be explained by a physician and that patients have ample opportunities to ask questions and review the information. Furthermore, it is important to discuss the chances that a patient may conceive spontaneously without ART. In fact, some investigators believe that ART services are overused and that some patients using ART could ultimately conceive on their own.[51] Information provided to patients should then be separated into what is considered part of the standard of care and what would be considered experimental.[52]

The American College of Obstetricians and Gynecologists recommends a thorough discussion of the risks of ART including the potential impact on perinatal outcomes. Significantly, given limited data, they did not make strict recommendations about reviewing the long-term health outcomes of offspring conceived from IVF.[53] According to the American Society of Reproductive Medicine, "ART patients have the right to self-

determination and must make the final decision as to what is appropriate and acceptable treatment in his or her particular situation."[54] The ESHRE Task Force on Ethics and Law acknowledges that the data are limited on outcomes for offspring conceived with ART but does not make a strict recommendation on how such information should be disseminated.[55]

In summary, what strategy should be adopted to consent ART patients?

While all patients should be fully informed prior to commencing ART, we believe that a key difference exists between infertile patients, who need to use ART as the only means to achieve pregnancy, and (likely) fertile patients who elect to use ART techniques as a family planning option.

While the risks of ART are similar for patients seeking ART electively and for those with true infertility, we suggest that the potential perinatal and long-term risks to offspring health be weighed more heavily amongst patients who choose to pursue ART electively. These are patients in whom possible harm to the offspring could be avoided by not using ART altogether. The benefits for infertility patients are the increased likelihood of conceiving genetically related children and/or carrying their child. For patients seeking care electively, ART provides them with a sense of security that they may be able to build their family at some point in the future. Elective ART carries the additional risks of pursuing treatment without an immediately known outcome, and the potential to expend resources on a treatment that may not be necessary if they are fertile. Arguably, there are more risks for people seeking elective ART and the different risk-benefit ratio for these patients ought to be addressed (Figure 3).

Some have argued that there is a conflict between the possible impact of ART on offspring health (non-maleficence) and the right to procreation (reproductive autonomy) for potential parents.[56],[53.] While the tension between non-maleficence towards potential children and parental autonomy is not limited to the health of ART offspring[57], we must be careful not to infringe on patients' procreative rights. One option would be to inform all patients about all potential risks. However, the crux of the matter is that the long-term health risks for children are only suggested and not shown with certainty. Therefore, it could be argued that discussing these risks as part of the informed consent process could create inappropriate and unrealistic anxiety. In fact, at least two hypothetical scenarios can be seen:

1. IVF children will have some long-term health problems and the parents were not informed of this possibility prior to conception.
2. IVF children will not have long term health problems and parents have been informed of potential long-term risk

In the first scenario, offspring of fertile patients who chose to use ART electively may be unnecessarily exposed to reproductive technologies, since the parents could have conceived spontaneously. In contrast, infertile patients do not have an option to choose, since infertility limits conception. The alternative for people with infertility would be not to have children at all. In the second scenario, prospective parents would be inappropriately concerned.

Overall, we believe that the emerging human and animal evidence pointing to a possible increase in chronic health conditions in ART children should be discussed with all prospective parents, with special emphasis to patients planning to electively use ART. Consenting guidelines should be developed by professional societies and funding made available for research using animal models and on epidemiological studies on the health of ART children.

One approach to addressing the risks of ART on offspring with patients may be to review that:

1. ART is elective
2. For many, ART results in the live birth of children that are considered generally healthy
3. The long-term impacts of ART are unknown but there are some data to suggests that children conceived with ART may be at increased risk for chronic disease
4. Adverse neonatal and childhood outcomes from ART are overall rare and the risks for chronic disease may be modified with lifestyle choices, therefore, when ART is the only option for conception, the benefits outweigh the risks

4. Conclusion

Global utilization of ART has grown exponentially since the first IVF was performed and continued growth is anticipated. With an estimated 8 million people conceived from ART, this technology has been appropriately deemed safe. However, a growing body of literature suggests that there may be increased risks of perinatal morbidity and long-term health consequences for offspring born from ART. Such risks, may need to be more heavily considered amongst people seeking elective gamete or embryo cryopreservation or who are seeking ART without an infertility diagnosis. Including a discussion about the potential long-term outcomes of ART requires balancing the potential impact of such information without causing undue anxiety. Given the ever evolving nature of the ART field, it is time to address the possibility of long term health complications with all patients, but with particular attention to patients choosing ART electively.

Acknowledgments

The authors wish to thank Dr Elena Gates for her insightful comments to the manuscript.

This work was partially funded by R01 HD092267-01 to PR

References

1. In-Vitro Fertilization: The Pioneers' History. (Cambridge University Press, 2018). doi:10.1017/9781108551946
2. Adamson GD, Tabangin M, Macaluso M & de Mouzon J The number of babies born globally after treatment with the assisted reproductive technologies (ART). Fertil. Steril 100, S42 (2013).
3. Adamson GD et al. International Committee for Monitoring Assisted Reproductive Technologies (ICMART) World Report on ART, 2014 and The International Glossary on Infertility and Fertility Care, 2017. (2018).

4. ESHRE. ESHRE: ART fact sheet. (2018).
5. Faddy MJ, Gosden MD & Gosden RG A demographic projection of the contribution of assisted reproductive technologies to world population growth. Reprod. Biomed. Online 36, 455–458 (2018). [PubMed: 29503211]
6. Reindollar RH et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil. Steril 94, 888–899 (2010). [PubMed: 19531445]
7. Glenza J Fertility and canapés: why egg freezing parties are a hot item on Wall St. The Guardian (2018).
8. Mature oocyte cryopreservation: a guideline. Fertil. Steril. 99, 37–43 (2013). [PubMed: 23083924]
9. Hammarberg K et al. Reproductive experiences of women who cryopreserved oocytes for non-medical reasons. Hum. Reprod. Oxf. Engl 32, 575–581 (2017).
10. US Dept of Health and Human Services. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2016 Assisted Reproductive Technology Preliminary National Summary Report (2016).
11. Baldwin K, Culley L, Hudson N, Mitchell H & Lavery S Oocyte cryopreservation for social reasons: demographic profile and disposal intentions of UK users. Reprod. Biomed. Online 31, 239–245 (2015). [PubMed: 26099440]
12. Kushnir VA, Barad DH, Albertini DF, Darmon SK & Gleicher N Effect of Embryo Banking on U.S. National Assisted Reproductive Technology Live Birth Rates. PLOS ONE 11, e0154620 (2016). [PubMed: 27159215]
13. Feuer SK, Camarano L & Rinaudo PF ART and health: clinical outcomes and insights on molecular mechanisms from rodent studies. Mol. Hum. Reprod 19, 189–204 (2013). [PubMed: 23264495]
14. Luke B, Gopal D, Cabral H, Stern JE & Diop H Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology. Am. J. Obstet. Gynecol 217, 327.e1–327.e14 (2017). [PubMed: 28400311]
15. Pinborg A et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum. Reprod Update 19, 87–104 (2013).
16. Wadhwa PD, Buss C, Entringer S & Swanson JM Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin. Reprod. Med 27, 358–368 (2009). [PubMed: 19711246]
17. Biechele S, Lin C-J, Rinaudo PF & Ramalho-Santos M Unwind and transcribe: chromatin reprogramming in the early mammalian embryo. Curr. Opin. Genet. Dev 34, 17–23 (2015). [PubMed: 26183187]
18. Reik W Stability and flexibility of epigenetic gene regulation in mammalian development. Nature 447, 425–432 (2007). [PubMed: 17522676]
19. Doherty AS, Mann MR, Tremblay KD, Bartolomei MS & Schultz RM Differential effects of culture on imprinted H19 expression in the preimplantation mouse embryo. Biol. Reprod 62, 1526–1535 (2000). [PubMed: 10819752]
20. Manipalviratn S, DeCherney A & Segars J Imprinting disorders and assisted reproductive technology. Fertil. Steril 91, 305–315 (2009). [PubMed: 19201275]
21. Bloise E et al. Impaired placental nutrient transport in mice generated by in vitro fertilization. Endocrinology 153, 3457–3467 (2012). [PubMed: 22562173]
22. Duranthon V & Chavatte-Palmer P Long term effects of ART: What do animals tell us? Mol. Reprod. Dev 85, 348–368 (2018). [PubMed: 29457303]
23. Alberto MLV et al. Development of bovine embryos derived from reproductive techniques. Reprod. Fertil. Dev 25, 907–917 (2013). [PubMed: 22953743]
24. Ecker DJ et al. Long-term effects of culture of preimplantation mouse embryos on behavior. Proc. Natl. Acad. Sci. U. S. A 101, 1595–1600 (2004). [PubMed: 14747652]
25. Fernández-Gonzalez R et al. Long-term effect of in vitro culture of mouse embryos with serum on mRNA expression of imprinting genes, development, and behavior. Proc. Natl. Acad. Sci. U. S. A 101, 5880–5885 (2004). [PubMed: 15079084]

26. Watkins AJ et al. Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure. Proc. Natl. Acad. Sci. U. S. A 104, 5449–5454 (2007). [PubMed: 17372207]
27. Rexhaj E et al. Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span. J. Clin. Invest 123, 5052–5060 (2013). [PubMed: 24270419]
28. Donjacour A, Liu X, Lin W, Simbulan R & Rinaudo PF In vitro fertilization affects growth and glucose metabolism in a sex-specific manner in an outbred mouse model. Biol. Reprod 90, 80 (2014). [PubMed: 24621920]
29. Feuer SK et al. Sexually dimorphic effect of in vitro fertilization (IVF) on adult mouse fat and liver metabolomes. Endocrinology 155, 4554–4567 (2014). [PubMed: 25211591]
30. Sommovilla J, Bilker WB, Abel T & Schultz RM Embryo culture does not affect the longevity of offspring in mice. Reproduction 130, 599–601 (2005). [PubMed: 16264090]
31. Chen M & Heilbronn LK The health outcomes of human offspring conceived by assisted reproductive technologies (ART). J. Dev. Orig. Health Dis 8, 388–402 (2017). [PubMed: 28416029]
32. Ceelen M, van Weissenbruch MM, Vermeiden JPW, van Leeuwen FE & Delemarre-van de Waal HA Cardiometabolic differences in children born after in vitro fertilization: follow-up study. J. Clin. Endocrinol. Metab 93, 1682–1688 (2008). [PubMed: 18285409]
33. Guo X-Y et al. Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis. Fertil. Steril 107, 622–631.e5 (2017). [PubMed: 28104241]
34. Meister TA et al. Association of Assisted Reproductive Technologies With Arterial Hypertension During Adolescence. J. Am. Coll. Cardiol 72, 1267–1274 (2018). [PubMed: 30190005]
35. Seggers J et al. Is ovarian hyperstimulation associated with higher blood pressure in 4-year-old IVF offspring? Part I: multivariable regression analysis. Hum. Reprod. Oxf. Engl 29, 502–509 (2014).
36. Kuiper D et al. Cardiovascular health of 9-year-old IVF offspring: no association with ovarian hyperstimulation and the in vitro procedure. Hum. Reprod. Oxf. Engl 32, 2540–2548 (2017).
37. Scherrer U et al. Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies. Circulation 125, 1890–1896 (2012). [PubMed: 22434595]
38. Chen M et al. Altered glucose metabolism in mouse and humans conceived by IVF. Diabetes 63, 3189–3198 (2014). [PubMed: 24760136]
39. Gkourogianni A et al. Plasma metabolomic profiling suggests early indications for predisposition to latent insulin resistance in children conceived by ICSI. PloS One 9, e94001 (2014). [PubMed: 24728198]
40. Wall RJ & Shani M Are animal models as good as we think? Theriogenology 69, 2–9 (2008). [PubMed: 17988725]
41. Hewitson L Primate models for assisted reproductive technologies. Reprod. Camb. Engl 128, 293–299 (2004).
42. Carter AM Animal models of human placentation--a review. Placenta 28 Suppl A, S41–47 (2007). [PubMed: 17196252]
43. Bay B, Mortensen EL, Hvidtjorn D & Kesmodel US Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study. BMJ 347, f3978–f3978 (2013). [PubMed: 23833075]
44. Reigstad MM et al. Risk of Cancer in Children Conceived by Assisted Reproductive Technology. Pediatrics 137, e20152061 (2016). [PubMed: 26908669]
45. Hall S The Cut: A New Last Chance There could soon be a baby-boom among women who thought they'd hit an IVF dead end. N. Y. Mag (2017).
46. Treff NR, Forman EJ & Scott RT Next-generation sequencing for preimplantation genetic diagnosis. Fertil. Steril 99, e17–18 (2013). [PubMed: 23481279]
47. Capelouto SM, Archer SR, Morris JR, Kawwass JF & Hipp HS Sex selection for non-medical indications: a survey of current pre-implantation genetic screening practices among U.S. ART clinics. J. Assist. Reprod. Genet 35, 409–416 (2018). [PubMed: 29080968]

48. Collier AC, Miyagi SJ, Yamauchi Y & Ward MA Assisted reproduction technologies impair placental steroid metabolism. J. Steroid Biochem. Mol. Biol 116, 21–28 (2009). [PubMed: 19406239]

49. de Waal E et al. In vitro culture increases the frequency of stochastic epigenetic errors at imprinted genes in placental tissues from mouse concepti produced through assisted reproductive technologies. Biol. Reprod 90, 22 (2014). [PubMed: 24337315]

50. Madeira JL, Coyne K, Jaeger AS, Parry JP & Lindheim SR Inform and consent: more than just “sign here”. Fertil. Steril 108, 40–41 (2017). [PubMed: 28434753]

51. Kamphuis EI et al. Are we overusing IVF? BMJ 348, g252–g252 (2014). [PubMed: 24472708]

52. New york State Task Force on LIfe and the Law. Informed Consent for In Vitro Fertilization and Related Procedures: Practioner’s guide to using the model form.

53. American College of Obstetricians and Gynecologists. Perinatal risks associated with assisted reproductive technology. Committee Opinion No. 671. Obstet Gynecol e61–8 (2016). [PubMed: 27548556]

54. Revised minimum standards for practices offering assisted reproductive technologies: a committee opinion. Fertil. Steril. 102, 682–686 (2014). [PubMed: 24954775]

55. ESHRE Task Force on Ethics and Law including et al. ESHRE Task Force on Ethics and Law 13: the welfare of the child in medically assisted reproduction. Hum. Reprod 22, 2585–2588 (2007). [PubMed: 17728354]

56. Child-rearing ability and the provision of fertility services: a committee opinion. Fertil. Steril. 100, 50–53 (2013). [PubMed: 23481278]

57. Roy M-C, Dupras C & Ravitsky V The epigenetic effects of assisted reproductive technologies: ethical considerations. J. Dev. Orig. Health Dis 8, 436–442 (2017). [PubMed: 28535841]

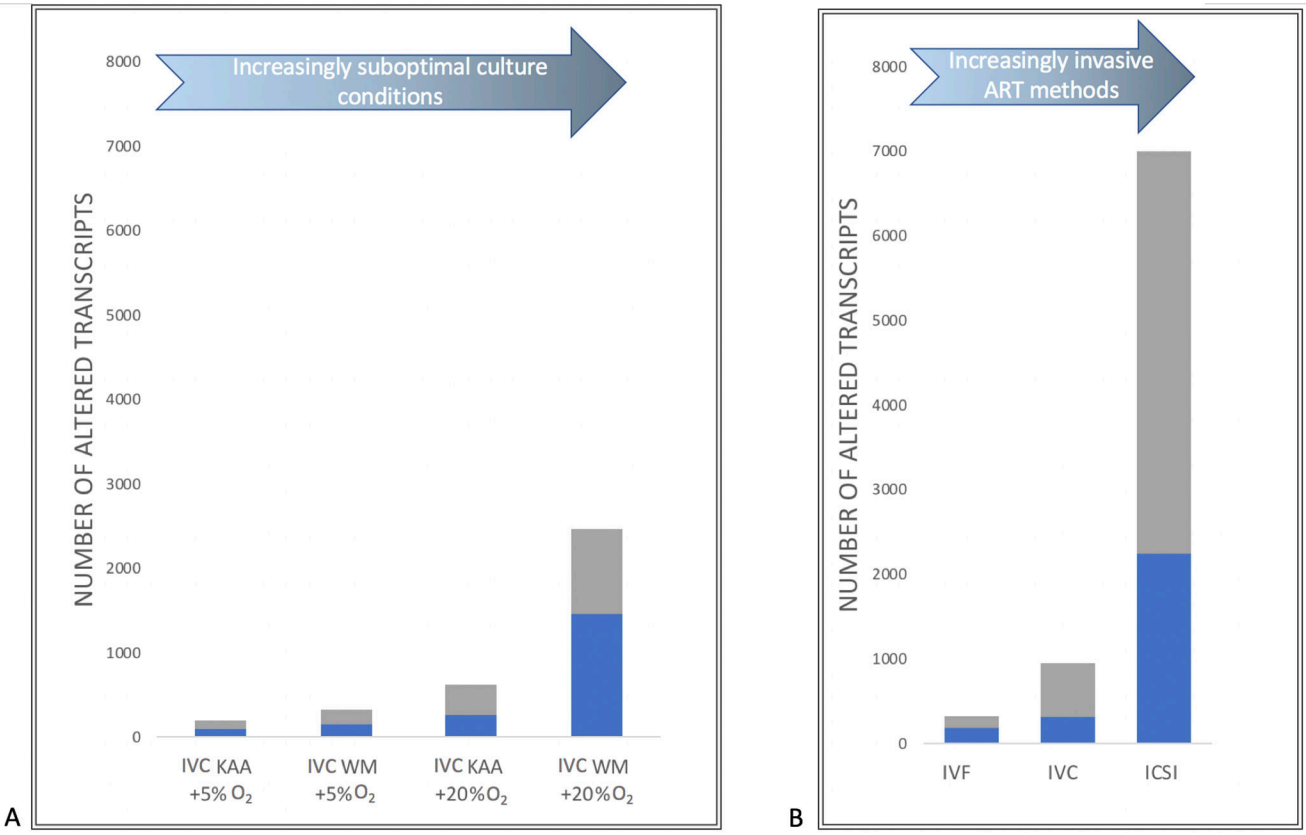
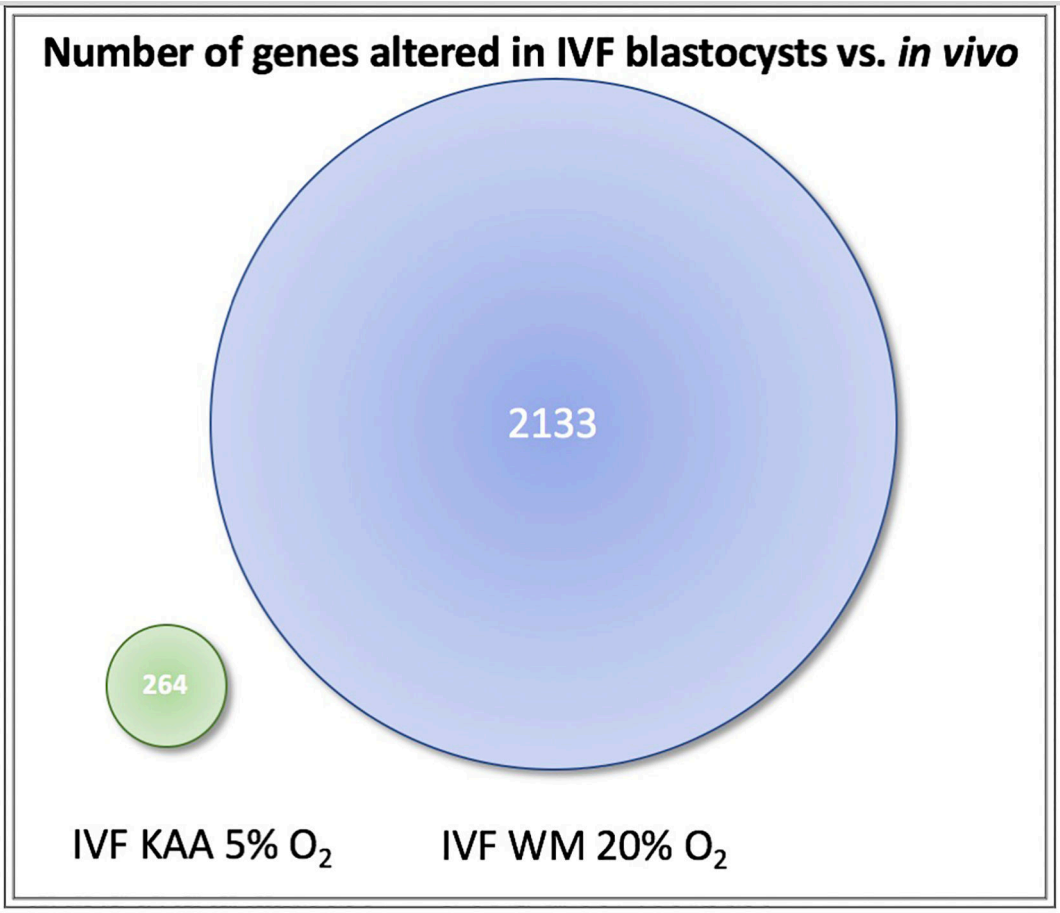


Figure 1.

(Modified from Feuer et al. 2016) **A.** Increasing suboptimal culture conditions result in a proportional increase in abnormalities of gene expression in blastocysts. Mouse zygotes, after spontaneous conception, were flushed out of the uterus and cultured in different media with different oxygen concentrations (5% or 20% Oxygen). KAA - potassium simplex optimization medium supplemented with amino acids. WM – Whitten's Medium. **B.** Increasingly abnormal gene expression in murine blastocysts fertilized with different techniques. IVF = in vitro fertilization; IVC= in vitro culture (of zygote to the blastocyst stage); ICSI= intracytoplasmic sperm injection. All blastocysts were cultured in the same condition (WM and 20% oxygen). Of note, in this study the IVC blastocysts have more abnormal gene expression than IVF blastocyst. This can be explained because the change of environment (from *in vivo* to *in vitro*) is more stressful to the embryo than being exposed to the same culture conditions for the whole time.



Metabolic parameters in murine offspring born from IVF blastocysts vs. *in vivo*

	IVF KAA 5% O2	WM 20% O2
IP GTT	Normal	Abnormal
Growth	Normal	Abnormal
Beta Cells	Affected	Not tested

Figure 2.

(Data are from Feuer et al 2014 and Donjacour et al, 2014) **A**. Compared to in vivo flushed mouse blastocysts, blastocysts cultured in suboptimal culture medium (WM and 20% O_2) have a nearly 10 fold increase of misexpressed genes compared to blastocysts cultured using an optimal medium (KAA and 5% O_2). Of note, the area of the circle is proportional to the number of altered genes. **B.** Table reflecting adult metabolic phenotypes of murine concepti cultured in different media conditions. Importantly, mouse offspring cultured in stressful

conditions (WM and 20% O_2) had more severe alterations of the adult metabolic phenotype compared to offspring cultured with optimal medium (KAA 5% and 5%O_2).

WM – Whitten's Medium; KAA - Potassium simplex optimization medium supplemented with amino acids; IP GTT: intraperitoneal glucose tolerance test.

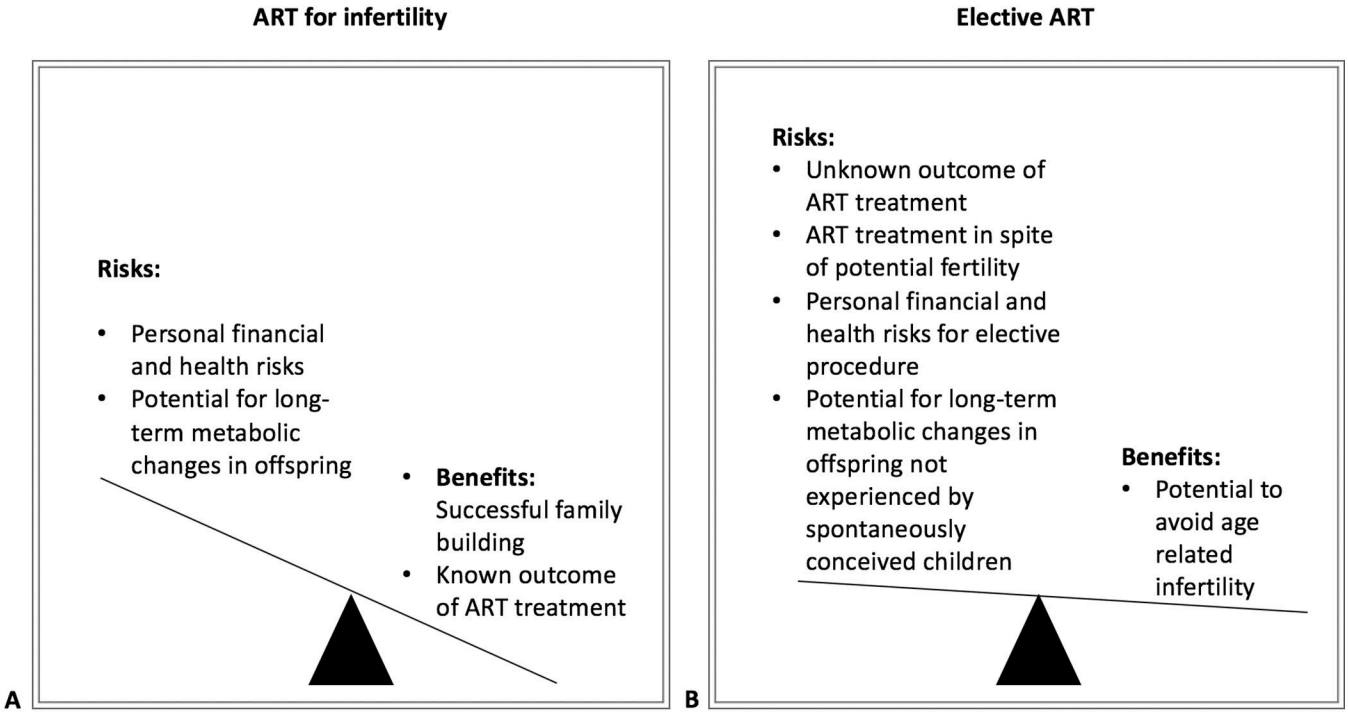


Figure 3.

The Risks and Benefits of ART for people requiring treatment compared to those using ART electively. **A**. Amongst people with infertility, the benefits of ART (including potential successful family building and a known outcome from treatment) greatly outweigh the risks to the intended parent and potential offspring. **B**. For people seeking elective ART, the benefits of treatment, namely the avoidance of age related-infertility may be more balanced with the risks of ART.