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Published in:
Yale Journal of Biology and Medicine

YALE JOURNAL OF BIOLOGY AND MEDICINE 91 (2018), pp.225-235.

ORIGINAL CONTRIBUTION

YJBM

Effects of Conception Using Assisted Reproductive Technologies on Infant Health and Development: An Evolutionary Perspective and Analysis Using UK Millennium Cohort Data

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Millions of infants around the world have been born as a result of assisted reproductive technologies (ART†), and in the past three decades ART has become increasingly effective and technologically sophisticated. At the same time, advances have been made in understanding the evolutionary biology of mate choice and post-copulatory processes. These advances have relevance for ART as ART methods to a greater or lesser extent circumvent potentially important natural processes determining which fertilized embryo is successfully implanted. Here, using UK Millennium cohort data, the hypothesis that ART methods which circumvent both natural *in vivo* selection of ova and sperm (for example *in vitro* fertilization) lead to poorer child health and developmental outcomes than ART methods in which fertilization occurs naturally after fertility treatment using drugs or diathermy. The results showed that both groups of ART were associated with the number of infant health problems from birth through the first week of life when compared with naturally conceived infants. Methods with artificial fertilization were associated with two of the four most common health conditions: respiratory distress (OR 1.80; 95% CI 1.12-2.91) and infections (OR 1.77; 95% CI 1.96-2.06). ART methods with artificial fertilization were associated with delayed achievement of developmental milestones at nine months, and when contrasted with ART using fertility drugs or diathermy only, were significantly more likely to be associated with slower child development. This suggests that evolved processes that determine which egg and sperm lead to successful pregnancy may be important for offspring quality as indicated by infant development. Clinically, the results suggest that women should avoid ART with artificial gamete selection if they can conceive using other ART methods.

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†Abbreviations: ART, assisted reproductive technologies; IVF, *in vitro* fertilization; MHC, major histocompatibility complex.

Keywords: *In vitro* fertilization, IVF, mate choice, natural selection, developmental milestones, respiratory distress, infections, reproduction

INTRODUCTION

Assisted reproductive technology (ART) refers to a number of procedures aimed at establishing pregnancy in women who have been unable to, or who choose not to become pregnant naturally via sexual intercourse. The technologies range from drugs which stimulate the pituitary to induce ovulation, to surgical intervention. Commonly used ART methods are summarized in Table 1. These methods have led to successful births for millions of women, many of whom could not have conceived naturally.

With the rapid uptake of ART there were soon enough babies born using these technologies for researchers to be able to assess whether they led to an increased risk of adverse pregnancy outcomes. Systematic reviews and large studies have uncovered a number of adverse outcomes of ART. Meta-analyses have shown relative risks of low birthweight, perinatal mortality, and neonatal admissions to intensive care that are around 1.5 times greater than for non-ART births [1,2]. Given these findings, research has shifted to the question of *which* ART technologies or processes lead to adverse perinatal outcomes. These questions include whether freezing embryos versus using fresh for *in vitro* fertilization is associated with increased risks; whether more modern techniques reduce perinatal risks, and what stage of development the blastocyst is at retrieval for use in IVF [2,3]. Consistent results have not yet emerged from these studies, for example, embryos harvested at the blastocyst stage rather than the earlier cleavage stage appear to have some adverse and some positive perinatal outcomes for the infant [4].

Studies of which ART processes and technologies are safest in terms of perinatal and later child health and development have focused on timing and technology. However, the focus of the present paper is to step back from the details of ART technology to think about reproductive biology and evolution more generally: since the advent of and increasing use of ART technologies, more is known about reproductive processes that are relevant to the question of which ART method should be the safest.

Evolutionary Processes and Why They Are Important for Thinking About ART

Evolutionary processes have resulted in an array of traits influencing which sperm fertilizes which egg: fertilization is not a random process where any healthy sperm is equally likely to fertilize any healthy egg. These evolved processes fall into two categories: mate selection and post-copulatory processes. Both sets of processes are multifaceted, complex, and much is unknown. The next two sections provide an outline of them, followed by what existing knowledge implies for which types and why ART is likely to be associated with adverse birth and childhood outcomes.

Mate Choice

Evolution has selected for the expression of signals which demonstrate the genetic quality of an individual, as well as for the ability to recognize them as cues to genetic quality, or as sexually attractive characteristics. In addition to signaling genetic quality, genetic compatibility between mates plays a role in human mate selection. While men selected as sperm donors can be selected for their physical attractiveness and lack of genes associated with some diseases, genetic compatibility is a more difficult problem for ART. Mate choice for genetic compatibility can be divided into two distinct types: avoidance of inbreeding by selecting sexual partners who are not close genetic relatives, and selection for the optimal interaction between paternal and maternal genomic contributions to offspring [5]. Major histocompatibility complex (MHC) alleles determine key aspects of offspring immunity. Heterozygosity for MHC alleles is beneficial for immune system recognition of pathogens: heterozygous individuals are able to mount an immune response to a greater variety of pathogens than homozygous individuals [6]. In humans there is evidence that women prefer the scent of men with different MHC profiles to their own [7,8] and report greater relationship satisfaction or attraction to their sexual partner [9,10]. Population-based studies of whether couples are more MHC-dissimilar than would be predicted by chance alone have shown more mixed results, but overall suggest that humans prefer partners who are heterozygous for MHC alleles [11].

Women seeking sperm from a donor using a sperm bank usually receive sperm from men who have been screened for some genetic diseases and infections (such as HIV), and receive reported information about age and personality traits, but the donor selection system does not ensure genetic compatibility by MHC haplotyping. Additionally, selecting sperm for use in ART which is genetically dissimilar from the recipient of the sperm both to avoid deleterious effects of inbreeding and matching MHC profiles is not an insurmountable problem to solve.

Post-Copulatory Processes

The second aspect of the evolution of reproductive processes that ART technologies circumvent is post-copulatory sperm selection by females, and sperm competition. It is in a woman's reproductive interest only to let competent sperm of a preferred partner reach and fertilize her ovum. Female selection of sperm is theoretically possible as soon as sperm are ejaculated into the vagina: vaginal pH is typically around 5 or less, which is protective against pathogens including sexually transmitted infections. Vaginal pH rapidly increases when in contact

Table 1. Commonly used assisted reproductive technologies (ART) and their acronyms.

Treatment name	Description	Gamete origin and selection
Clomifene citrate	Stimulates pituitary to release GnRH, resulting in the release of multiple eggs	Own gametes, fertilization occurs naturally
Diathermy	Laparoscopic drilling into ovary to induce ovulation	
IUI	Intrauterine sperm injection of partner's sperm	Own gametes, assisted gamete selection
ICSI	IVF with intra-cytoplasmic sperm injection directly into egg, usually using partner's sperm	
DI	Injection of donor sperm directly into uterus	Gamete origin varies, assisted gamete selection
GIFT	Gamete intra-fallopian tube transfer	
IVF	*In vitro* fertilization	
Frozen embryo transfer	Implantation of fertilized embryo	

with seminal fluid [12]. The vagina additionally contains immune cells, such as leukocytes which can phagocytize sperm [13]. The small percentage of sperm that reach the cervix remain vulnerable to immunoglobulins in the cervical mucus, and to attack by neutrophils in the uterus [14]. In addition, sperm are assisted and guided through the female reproductive tract by a number of processes including contractions in the fallopian tubes and thermotaxis (see [15] for a thorough review of sperm transport in the female reproductive tract). Together, these mechanisms along with properties of sperm which serve to help evade attack by the female immune system, reach and fertilize the ovum, mean that fertilization is a non-random process that is far more complex than sperm selection procedures to obtain motile, normal sperm in ART.

Post-copulatory processes which allow sperm to be phagocytized or aid the passage of sperm may facilitate female choice of sperm such that the healthiest genetically compatible sperm are more likely to fertilize the ovum. However, some post copulatory processes may simply be associated with sperm competition between and within ejaculates, and with genomic conflicts that would not ultimately contribute to infant health outcomes. One example of genomic conflict which occurs in the female reproductive tract is of alleles which kill sperm which do not carry a particular allele [16]. This leads to the spread of an allele, but such processes are unlikely to lead to healthier pregnancies and offspring.

In response to new understandings of sperm morphology and transport in the female reproductive tract, new ART methods are being developed which serve to better mimic natural *in vivo* processes (for a review see [17]). The aim of these new methods is largely to increase the probability of successful fertilization in ART treatments, but they may also result in higher quality fetuses, fewer problems during pregnancy, and fewer health problems in children born via ART.

Study Predictions

Palomba *et al*. [18] tested the hypothesis that babies born using low technology ART interventions including Clomifene should have better perinatal health outcomes than those conceived using more invasive ART technologies simply due to potential technological inadequacies of invasive ART procedures. They used existing literature to address this hypothesis but found only limited support from the ART literature. If mate choice and sperm selection processes evolved as processes which maximize evolutionary fitness by influencing the survival and health of offspring, then it is likely that the greater the ART intervention, the greater the likelihood that offspring viability will be negatively impacted. For example, ART using fertility drugs such as Clomifene should result in better child outcomes than methods which additionally circumvent sperm selection in the female reproductive tract, such as IVF. In Table 1 above, two commonly used ART treatments, Clomifene and diathermy, stimulate ovulation but fertilization occurs naturally *in vivo*. The remaining ART techniques listed in Table 1 involve assisted gamete selection, circumventing natural post-copulatory processes. The prediction is that ART with assisted gamete selection will lead to poorer perinatal outcomes than when fertilization occurs naturally using ART interventions which stimulate ovulation with drugs or the surgical procedure ovarian diathermy. Circumventing mate choice for genetic compatibility in addition to assisted gamete selection, such as using donated sperm, should lead to the highest risk of infant health problems of all types of ART. However, the cohort study data used here does not contain a sufficient sample size for this analysis, and will be limited to contrasting stimulating ovulation followed by natural fertilization with ART using artificial fertilization.

Table 2. Descriptive statistics (n=18,552 births).

Variable	Min	Max	Mean	Std. Dev.
Fertility drugs or diathermy only	.00	1.00		n. yes = 199
ART with artificial gamete selection	.00	1.00		n. yes = 255
Numbers of births including participant	1	3	1.01	.12
Baby's age in days	243	382	295.49	15.25
Sex of baby 1=male 2=female	1	2		n. female = 9021 n. male = 9531
Birth weight in kg	.39	7.23	3.34	.59
Mother's birth year	1949	1987	1971.92	5.95
Mother's self-rated general health. 1=excellent to 4=poor	1	4	1.91	.74
Mother reported longstanding Illness 1=yes 2=no	1	2		n. yes = 3906
Socioeconomic class: McClements Score	.84	3.30	1.38	.29
Baby's n. health problems in 1st week	0	50	1.63	1.99
Baby's development: 1=often, 2=once or twice, 3=never				
Smiles	1	3	1.01	.08
Sits up	1	3	1.07	.32
Stands up holding on	1	3	1.47	.78
Hands together	1	3	1.21	.53
Grabs objects	1	3	1.01	.12
Holds small objects	1	3	1.15	.45
Passes a toy	1	3	1.07	.30
Walks a few steps	1	3	2.81	.52
Gives toy	1	3	1.52	.72
Waves bye-bye	1	3	1.91	.84
Extends arms	1	3	1.21	.50
Nods for yes	1	3	2.72	.62

METHODS

Population and Sample

The hypothesis was tested using data from the UK Millennium cohort, which consists of 18,552 babies born from September 2000 to August 2001 identified using universal child benefit records, which the family of every child born in the UK is entitled to. The Millennium Cohort, like the UK's prior cohort studies, is an interdisciplinary study following a birth cohort from infancy to death. A cohort profile of the UK Millennium cohort is available providing more detail about the sample and sampling methods [19].

Dependent Variables

Two dependent variables were selected using the first sweep of the Millennium Cohort study, when the children were around 9 months old. This sweep contains data about pregnancy, birth, and early childhood. The first dependent variable aimed to capture variation in health problems with the baby from birth through the first week of life. These included conditions such as breathing difficulties, jaundice, and infections. The neonatal health variable is the number of health problems that the baby had, reported by the natural mother. Sensitivity analyses were carried out for the most commonly occurring health conditions to explore whether certain types of health problems were associated with the ART categories.

The second dependent variable aimed to measure general developmental progress in the first 9 months of life. The maternal interview contained questions about whether the baby had reached cognitive and motor skills milestones by 9 months (at the time of interview). These included 12 questions about whether the baby was able to smile, sit unassisted, hold objects, stand, walk, and

Table 3. Parameter estimates for negative binomial regression analysis (Omnibus test Chi-Square = 271.91, df=9, p=0.00). Dependent variable is number of illnesses reported in the first week of post-natal life.

Parameter	B	Std. Error	95% CI	Wald Chi-Square	p
(Intercept)	-3.03	3.40	-9.47 to 3.41	.80	.37
Fertility drugs or diathermy only = 0, all other observations = 1	-.21	.08	-.38 to -.05	7.19	.01
ART with artificial gamete selection = 0, all other observations = 1	-.13	.05	-.28 to -.02	5.73	.02
McClements Score	-.19	.04	-.26 to -.13	27.17	.00
Mother's general health 1=excellent to 4=poor	.06	.01	.04 to .09	23.19	.00
Mother's longstanding Illness, 1=yes 2=no	-.20	.02	-.24 to -.15	75.36	.00
Mother's birth year	.00	.00	.00 to .01	2.01	.16
Baby's birthweight in kg	-.04	.02	-.07 to -.01	4.94	.03
Baby's sex, 1=male 2=female	-.13	.02	-.16 to -.09	52.11	.00
Number of births including participant	-.15	.06	-.30 to .00	5.44	.02
(Scale)	.89				

other similar questions. Principal components analysis was used to create a single variable representing general child developmental progress, and sensitivity analyses were carried out to attempt to capture whether there were specific aspects of development that are delayed in ART babies.

Independent Variables

The Millennium cohort questionnaire included use and type of ART resulting in the birth of the cohort member. Only seven instances of sperm donation were reported in the cohort, so it was not possible to adequately test the hypothesis that avoiding mate selection and post copulatory processes should lead to poorer birth outcomes. However, it was possible to create two dummy variables to denote whether fertilization was artificial or natural. Natural fertilization ART methods included fertility drugs (Clomifene) and diathermy, and the artificial fertilization dummy variable included all of the other ART methods listed in Table 1.

The Millennium cohort study provides a rich source of information for including potential confounders in the statistical analyses. As the cohort babies are not all the same age, their age in months was included as a covariate in the analyses of developmental milestones. Gestational age at birth and birth weight are likely to influence child health and development. These two variables are very closely associated with each other: birthweight increases with gestational age [20]. Here, birth weight alone was used to avoid multicollinearity in the regression models. Infant sex and whether the birth was a multiple birth were controlled for as binary variables. Several maternal and family environment control variables were included: socio-economic status was operationalized using the McClement's score, a statistic currently used by the British government to compare household living standards. McClement's score is a household income equivalence scale which adjusts household income for household composition based on the number of individuals in a household and their ages [21]. As it is very likely that older mothers used ART more than younger mothers, maternal birth year was included as a covariate. Two measures of maternal health were included: her self-rated health status, and a binary variable indicating whether she reported any longstanding illness.

Statistical Analysis

Because it is an integer count, it was expected that the number of health problems experienced by a baby in the first week of life would have a Poisson distribution which could be analyzed using Poisson regression [22]. In reality, the distribution, while consistent with a Pois-

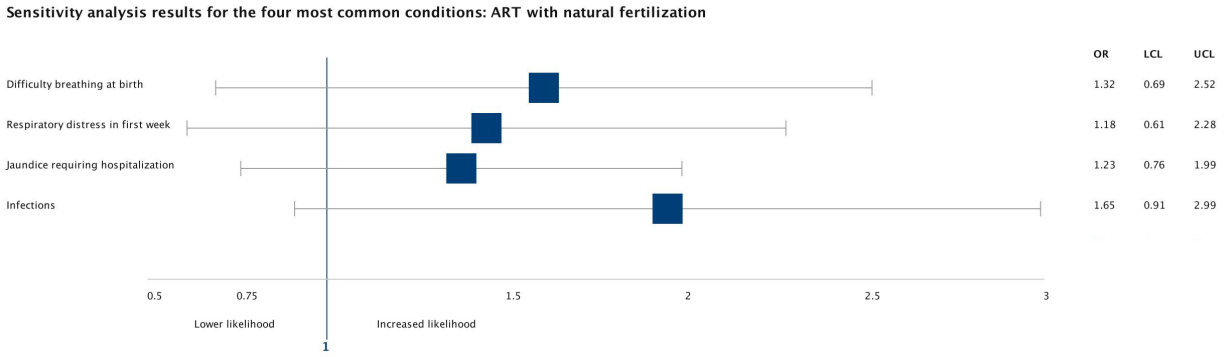

Figure 1. Forest plot visual summary of results of logistic regression models of the four most common health problems reported in the first week of post-natal life. The predictor variable shown is ART methods with natural fertilization (fertility drugs and diathermy). Odds ratios and 95% confidence intervals are displayed.

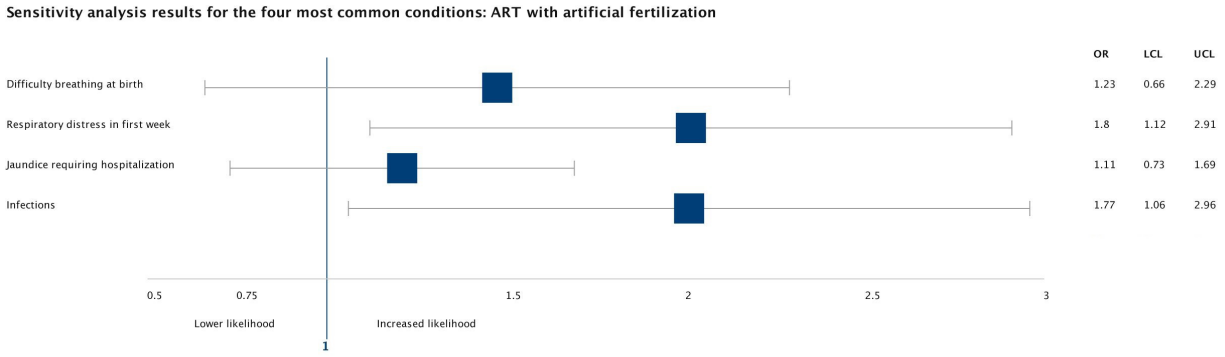

Figure 2. Forest plot visual summary of results of logistic regression models of the four most common health problems reported in the first week of post-natal life. The predictor variable shown is ART methods with artificial fertilization (IUI, ICSI, GIFT, IVF and frozen embryo transfer). Odds ratios and 95% confidence intervals are displayed.

son distribution in its overall shape, displayed over-dispersion of values, and negative binomial regression was carried out instead (in SPSS version 24). Multiple linear regression was used after principal components analysis to analyze variation in child developmental milestones.

Additional Analyses

Developmental milestones are known to vary within as well as between children: for example, children who smile early may not walk early. For this reason, as an additional analysis strategy, sensitivity analyses were carried out to determine which child development measures were most associated with the two ART categories. These were carried out as logistic regression analyses including all of the control variables. There were three levels to each maternal response about whether their child had reached each developmental milestone: "not yet", "sometimes", and "often". Additional sensitivity analyses were carried out to determine whether any of the most prevalent health problems in the first week of post-natal life were associated with ART individually. Results of the sensitivity analyses are presented using DistillerSR Forest Plot Generator from Evidence Partners and post hoc power analyses were carried out using G*Power 3.1.9.2.

The main analysis approach compared both groups of ART with outcomes for babies born without any ART intervention. As an additional analysis strategy, unpaired t-tests were carried out to determine whether the two ART groups differed in number of health problems in the first postnatal week, and the developmental milestones measure. To obtain normally distributed outcomes for the t-test examining the difference between the ART groups in number of health problems, Pearson standardized residuals were produced from a negative binomial regres-

Table 4. Results of multiple linear regression analysis of PCA score for all 12 developmental milestones. Higher values indicate later development. Model adjusted R-squared = 0.12.

	B	SE	Beta	t	p	95% CI
(Constant)	44.27	2.58		17.15	.00	
Fertility drugs or diathermy only	.02	.07	.00	.25	.81	-.12 to .15
ART with artificial gamete selection	.16	.06	.02	2.63	.01	.04 to .28
McClements Score	.08	.03	.02	2.94	.00	.03 to .13
Mother's general health 1=excellent to 4=poor	.00	.01	.00	.05	.96	-.02 to .02
Mother's longstanding Illness, 1=yes 2=no	-.02	.02	-.01	-1.15	.25	-.06 to .01
Mother's birth year	-.02	.00	-.12	-14.98	.00	-.02 to -.02
Numbers of births including participant	.28	.06	.03	4.79	.00	.17 to .40
Baby's age in days	-.02	.00	-.26	-37.47	.00	-.02 to -.02
Baby's sex, 1=male 2=female	-.20	.01	-.10	-14.40	.00	-.23 to -.17
Baby's birthweight in kg	-.27	.01	-.16	-22.12	.00	-.29 to -.24

sion of number of health problems including the control variables only as predictors.

RESULTS

Descriptive Statistics

Table 2 displays descriptive statistics for the study variables. 2.45% of the 18,552 babies in the cohort were born following the use of fertility drugs or ART methods in which fertilization was carried out artificially. The most commonly reported health problems from birth through the first week of life were, in order of frequency: jaundice requiring hospital treatment (n=1305 cases), delay in breathing at birth (n=765 cases), breathing difficulties or distress in the first week (n=689 cases), and infections (677 cases).

Health Problems in the First Week of Life

Results of the negative binomial regression analysis are displayed in Table 3. Both ART that relies on artificial fertilization and fertility treatments to induce ovulation were associated with a greater number of health problems recorded from birth through the first week of life. These results therefore do not support the hypothesis of more health problems with artificial fertilization, as both groups of treatments associate with infants' health problems. The measures of maternal health predicted the number of health problems experienced by neonates. Older mothers did not have an increased likelihood of having a child with health problems as a neonate. The results of the McClement's score variable showed that infants of mothers living in poverty experienced more health problems. One predictor did not produce results in the expected direction: babies who were born as one of twins or triplets had fewer, not more health problems as would be expected given that they were competing for maternal resources in pregnancy.

Sensitivity analyses of the four most common health conditions requiring hospitalization are shown in Figure 1 and Figure 2. Each line shown in Figures 1 and 2 represents a separate logistic regression analysis of whether the health condition was reported, including all covariates in the study. The trend for both categories of ART was towards more reported health conditions in the first week of post-natal life, but the odds of two of the four health conditions were significantly higher for infants born as a result of ART with artificial fertilization (see Figure 2). Although the sensitivity analysis results support the study hypothesis, it should be noted that they had modest statistical power to detect true effects: post hoc power analyses showed power of 0.81 for the largest odds ratios displayed in Figures 1 and 2, and 0.1 for the smallest.

A t-test to compare the two ART categories for the Pearson standardized residuals of number of health problems (from a negative binomial model including the control variables only) did not reveal a significant difference between groups (t=0.98, p=0.33).

Child Development in the First 9 Months

Principal components analysis of the 12 child developmental outcomes produced a stable factor solution (KMO = 0.75), and Bartlett's test showed that the correlations between developmental measures were different overall from zero ($p<0.0001$). The first principal component explained 19% of the variance and had an Eigenvalue of 2.29. It weighted each of the 12 developmental outcomes approximately equally. The scree plot suggested that the first principal component alone would be a suitable variable for use in statistical analysis, although

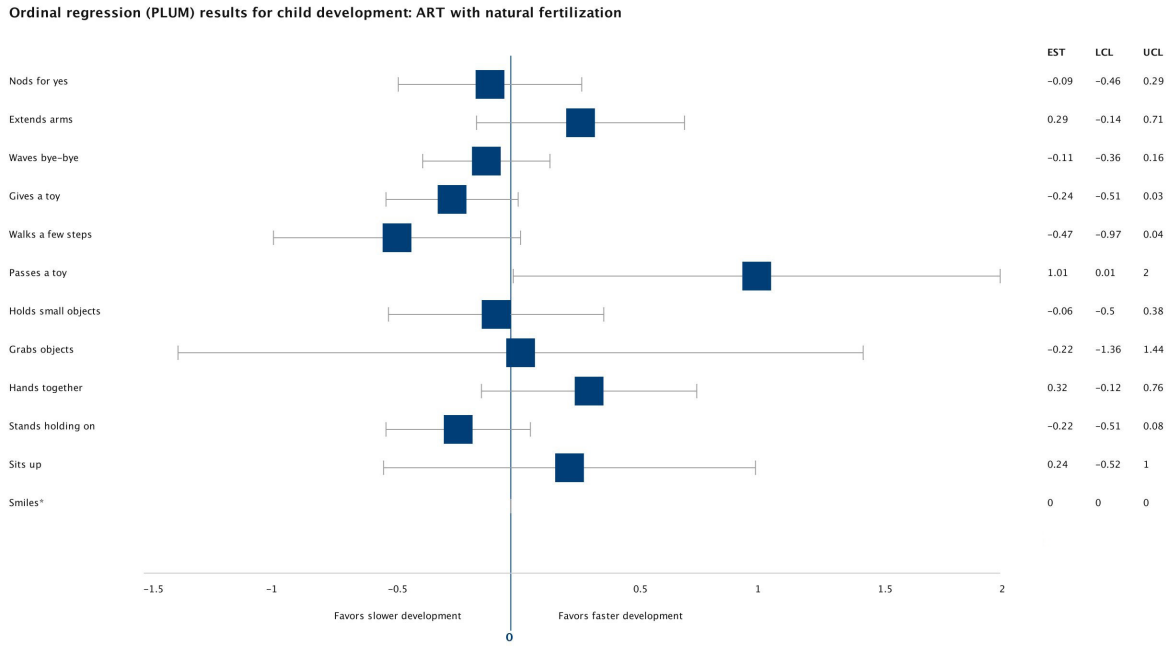

Figure 3. Forest plot visual summary of results of sensitivity analyses of child development measures. The predictor variable shown is ART methods with natural fertilization (fertility drugs and diathermy). Parameter estimates and 95% confidence intervals are displayed.

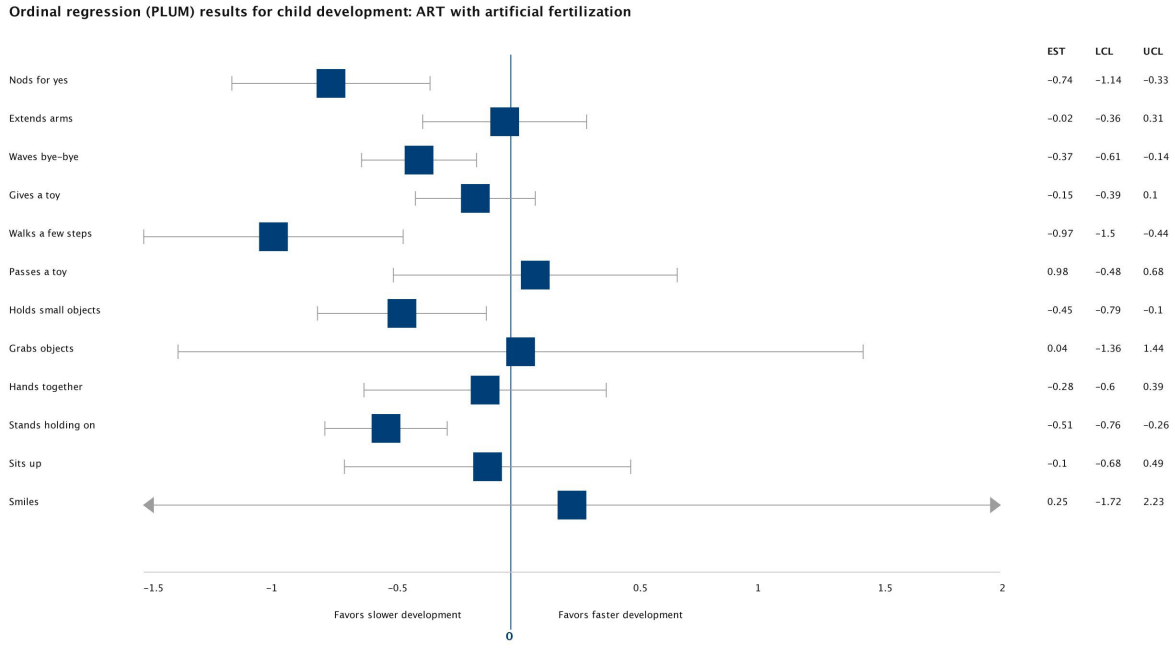

Figure 4. Forest plot visual summary of results of sensitivity analyses of child development measures. The predictor variable shown is ART methods with artificial fertilization (IUI, ICSI, GIFT, IVF and frozen embryo transfer). Parameter estimates and 95% confidence intervals are displayed.

two further Eigenvalues were just above one. Multiple regression analysis results of child development using the first principal component as the dependent variable are shown in Table 4. Babies born following ART treatments with artificial fertilization were less likely to have reached the developmental milestones. Consistent with the study hypothesis, babies born after fertility drugs or diathermy only did not show delayed development. The measures of mothers' health did not significantly predict development, but the other control variables significantly predicted later development: McClement's scores demonstrated delay in poorer households, and babies born to older mothers, with lower birthweights, and as multiple births were less likely to have reached the developmental milestones.

It is possible that ART affects some developmental outcomes more than others. For this reason, sensitivity analyses were carried using each of the 12 developmental measures separately. Results of ordinal regression models for the two types of ART are summarized using forest plots in Figure 3 and Figure 4. It should be noted that a smaller list of covariates was selected to address cell sample sizes that were too small in larger models. These covariates selected were the baby's age, sex, and McClement's score. One analysis was omitted due to not meeting the assumptions of ordinal regression, and this is marked with an asterisk in Figure 3. The results of the sensitivity analyses showed no clear pattern of particular groupings of developmental characteristics, such as standing and walking, being worse than others for ART babies. The results showed that fewer children born using ART technologies with artificial fertilization reached the developmental measures: nine of 12 tests were in the predicted direction, and of these five were statistically significant. The three tests which were not in the predicted direction were of measures which the vast majority of babies had achieved by 9 months old, and thus may not have contained sufficient variation.

Consistent with the main results, the t-test for differences between the ART categories in developmental delay showed significantly earlier development of milestones for babies born following ART using fertility drugs or diathermy only ($t=-2.42$, $p=0.016$).

SUMMARY AND DISCUSSION

Prior studies have explored negative health consequences of ART as problems inherent to the specific technologies [2-4,18]. Here a different approach was taken based on evolutionary theory and advances in understanding of fertilization. ART methods cannot replicate naturally occurring processes which determine which unions between male/female gametes are successful in establishing a pregnancy. This process is far more complex than a situation of any motile, normal sperm fertilizing any healthy egg. The prediction was made that infant health outcomes would be poorer following ART methods which circumvent a greater number of natural processes that occur between the time that sperm enters the female reproductive tract and successful fertilization.

Compared with natural fertilization and with ART which stimulated ovulation only, ART methods that included selection of sperm and/or egg in the clinic rather than by natural reproductive processes were associated with delayed achievement of developmental milestones in the first 9 months. Both groups of ART methods were associated with the number of infant health problems experienced in the first week, and no difference was found when directly comparing the two ART categories with each other. When the four most common perinatal health problems were analyzed separately, ART with artificial fertilization/gamete selection was associated with two of the four: breathing distress requiring hospitalization, and infections requiring hospitalization. ART with fertility treatment only was not significantly associated with any of the four.

The hypothesis did not predict that both forms of ART would have roughly equal effects on the number of health problems that infants had in their first week of post-natal life. One possible explanation is that stimulating ovulation using fertility drugs or diathermy leads to the fertilization of less viable eggs, which in turn results in the birth of infants with more health problems. However, ART methods which additionally rely on both harvesting eggs and selecting sperm in the clinic should theoretically lead to less viable fetuses because more evolved natural processes are being circumvented.

As stated at the beginning of this discussion, each ART method may have associated child health problems simply due to technical aspects of the procedure which may damage gametes, such as freezing and thawing. It is possible that the observed patterns are solely due to this, rather than to varying levels of bypassing evolved post-copulatory processes which influence offspring viability and health. However, a recent review of low versus high technology interventions did not support the hypothesis that child health outcomes are poorer with more invasive, high technology interventions [18].

Reviews of ART and perinatal health outcomes suggest that babies born after ART treatment have about one and a half times the risk of health problems compared with non-ART pregnancies [1,2]. The risks reported here are of a similar magnitude to those reported in past research (*e.g.,* see Figure 2). Perhaps the more important question is how the health risks and developmental delay associated with ART compare with other risk factors. Socio-economic class is a key predictor of infant development and mortality worldwide. In the UK, infants born to women in the highest quintile for socio-economic class

are around half as likely to die by four years old than those born to women in the lowest quintile [23]. The effects of ART with artificial fertilization found here are approximately comparable with the effects of moving down one quartile of the social class distribution and were not as large as the effects of being born with low birthweight.

The two groups of outcomes examined here, neonatal health problems and developmental delays, have been demonstrated to be associated with each other in prior research. In a systematic review of 153 studies of neonatal infections and other health insults, health insults in infancy were found to predict neurodevelopmental delay, with some of the largest effects found in gross motor and cognitive delay [24]. These developmental sequelae following neonatal health problems may result from life history energetic trade-offs between growth and development and immunity. For example, infants who must allocate more energy to immunity and tissue repair due to infection are likely to have less energy to allocate to growth and development.

This test of the hypothesis that ART which circumvents natural processes in mate selection and fertilization will lead to births of children with more health problems and developmental delay was hampered by small sample sizes of births using each ART approach: there were 454 ART births in total, but sample sizes for each specific ART method were often quite small, making analysis of each individual ART method separately not statistically justifiable. Future research with larger samples of, for example, pregnancies using sperm from donors who the mother had never met versus partners' sperm, would allow for more powerful and nuanced tests of the hypothesis. Second, ART techniques are regularly improved, and while much of this improvement may relate only to increasing the proportion of successful pregnancies, some may also improve outcomes for infants born using ART.

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