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OPINION

Is the wrong question being asked in infertility research?

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Abstract A persistent finding is that assisted reproductive technology (ART) is associated with compromised birth outcomes, including higher risks for prematurity, low birthweight, and congenital malformations, even among singletons. Over the past decade, our research group, the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART), has evaluated pregnancy and birth outcomes among three groups of women, those women treated with ART, those with indicators of subfertility but without ART treatment, and fertile women. We have also explored the influence of infertility-related diagnoses on outcomes for women and infants. Over the course of our research, we have changed our perspective from an original focus on ART treatment parameters as the primary cause of excess morbidity to one centered instead on the underlying infertility-related diagnoses. This paper summarizes the research findings from our group that support this change in focus for infertility-based research from a primary emphasis on ART treatment to greater attention to the contribution of preexisting pathology underlying the infertility and suggests directions for future analyses.

Keywords Assisted reproductive technology · Adverse pregnancy outcomes · Women's health · Child health

Capsule This review presents evidence that infertility research should focus on underlying pathology rather than treatment parameters as the major cause of compromised outcomes.

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Introduction

Since the early years of this century, assisted reproductive technology (ART) has been reported to be associated with compromised birth outcomes, including higher risks for prematurity, low birthweight, and congenital malformations, even among singletons [1–6]. With few exceptions, these studies have used control populations consisting of spontaneous deliveries to fertile couples. This has been the case, in spite of the fact that it has long been hypothesized that underlying subfertility might be as important in the etiology of these compromised outcomes as is ART. In the USA, evaluating the health of these children has been identified as a priority by both scientific and legislative groups [7–11]. However, these calls for study have failed to prioritize the study of specific subfertile comparison groups. For example, the most recent RFA from NIH (PAR-14-272, *Medically Assisted Reproduction*: *Investigation of Mechanisms Underlying the Adverse Outcomes and Development of New and Improved Methods to Overcome the Adverse Outcomes*) calls for studies on outcomes of ART along with use of a comparison group of non-IVF fertility (NIVF) treatments. These treatments are suggested without specific regard for the variety of possible causes of the underlying subfertility.

Over the past decade, our collaborative, the Massachusetts Outcomes Study of Assisted Reproductive Technology (MOSART), has conducted a series of analyses of maternal-child health using clinical ART data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) longitudinally linked to Massachusetts vital records and administrative data in the Pregnancy to Early Life Longitudinal (PELL) data system. As part of these studies, we created a subfertility measure through a combination of information from birth certificate checkboxes, diagnosis codes of infertility during hospitalizations and prior use of ART which allowed for identification of women with indicators of subfertility who did not receive ART treatment for the index delivery [12]. Other of our studies compared outcomes resulting from specific diagnoses that might contribute to subfertility [13, 14]. The addition of these comparison groups has, in the course of multiple analyses, changed our perspective from an original focus on ART treatment as the primary cause of excess morbidity to one centered instead on the underlying infertility-related diagnoses.

We are not the first researchers to posit subfertility as the primary etiology of poorer outcomes in ART births [15–20], but our ability to examine a range of outcomes with a subfertility comparison group in a contemporary US context utilizing a large multi-year population database provides a unique perspective on the health consequences of *both* subfertility and ART. Over time, we have developed a new hypothesis that, with the exception of higher rates of multiple pregnancies from ART and associated prematurity, underlying infertility-related diagnoses are the major effectors of excess morbidity for women and their children in this population. In this paper, we summarize some of our previously published findings that have led us to change our perspective and we suggest that researchers consider this paradigm shift when developing research on infertility.

ART as a cause of morbidity in women and children

It is well known that ART leads to an excess of multiple pregnancy and multiple birth and that this drives infant and maternal morbidity following ART. In our studies, we found that only three specific ART treatment effects contribute to excess perinatal morbidity in ART pregnancies: (1) plurality at birth, (2) plurality at conception, and (3) the number of embryos transferred. Through a series of analyses, adjusting for parental demographic characteristics, medical and reproductive history factors, and ART treatment parameters, we demonstrated that higher plurality at birth results in a more than tenfold increase in the risks for prematurity and low birthweight greater among twins versus singletons (AOR 11.84, 95 % CI 10.56, 13.27 and AOR 10.68, 95 % CI 9.45, 12.08, respectively) [21]. Plurality at 6-week gestation greater than plurality at birth (indicating fetal loss) was also associated with greater risks for low birthweight, prematurity, and small-for-gestational age outcomes in both singleton and twin births [21–24].

Even when plurality at conception and at birth are the same, the transfer of excess embryos is associated with significantly greater risks of moderate growth restriction in singleton as well as twin births [25]. Factors associated with transferring a higher number of embryos reflect suboptimal maternal conditions such as the use of autologous oocytes in women of older ages, less favorable oocyte or embryo quality, less favorable prognosis, or unsuccessful prior cycles (the use of micromanipulation, embryos which were thawed or cleavage-stage) [24]. The number of embryos transferred is significantly associated with plurality at 6-week gestation, which in turn is associated with greater risks for prematurity and low birthweight [24].

Only two other ART treatment parameters had any significant, adverse effects when adjusted for number of embryos transferred: the use of donor oocytes and thawed embryos. The use of donor versus autologous oocytes was associated with an increase in the risks for pregnancy-induced hypertension and prematurity (Table 1). The use of thawed versus fresh embryos was associated with higher risks for pregnancy-induced hypertension, but lower risks for low birthweight and small-for-gestation birthweight.

Table 1 Risks of adverse pregnancy outcomes by ART treatment parameters

ART parameter	Groups	AOR (95 % CI)[a]				
		Pregnancy hypertension	Gestational diabetes	Prematurity	Low birthweight	Small for gestation
Oocyte	Autologous	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Source	Donor	*1.87* (*1.45*, *2.42*)	1.24 (0.89, 1.72)	*1.43* (*1.11*, *1.83*)	1.24 (0.95, 1.62)	0.90 (0.64, 1.27)
Embryo	Fresh	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
State	Thawed	*1.30* (*1.08*, *1.57*)	0.99 (0.78, 1.25)	1.12 (0.94, 1.33)	*0.79* (*0.65*, *0.96*)	*0.38* (*0.28*, *0.53*)

Adapted from [21]; italicized values are significant; data from 2004–2008

[a] Models adjusted for maternal and paternal ages, race and ethnicity, education; infertility diagnoses,; maternal preexisting medical conditions (chronic hypertension and diabetes mellitus); plurality at 6 weeks gestation and at birth; oocyte source; semen source; ICSI; AZH; embryo state; number of embryos transferred

Subfertility and infertility-related diagnoses as causes of morbidity in children and women

Child health outcomes

We examined perinatal outcomes, controlling for parental demographic characteristics, medical and reproductive history factors, and ART treatment parameters, ART singleton births were at higher risk for preterm birth and low birthweight compared to subfertile births, but at comparable or lower risk for small-for-gestation birthweight and perinatal mortality (Table 2). Among twins, births to both fertile and ART-treated mothers had substantially lower rates of perinatal mortality than births to mothers with subfertility indicators [26].

We also examined pregnancy and birth outcomes by several infertility-related diagnoses among women in our study cohort, with and without ART treatment, and compared them to outcomes among fertile women [14]. As shown in Table 3, most children born to women with infertility-related diagnoses experienced significantly higher risks for premature birth and low birthweight, regardless of the presence or absence of ART treatment.

When we examined child outcomes within the study cohort of singletons and twins treated with ART, using pregnancies with male factor only as the reference group, women with the diagnoses of ovulation disorders and other factors were more likely to deliver preterm (AOR 1.47, 95 % CI 1.14, 1.89 and AOR 1.33, 95 % CI 1.05, 1.67, respectively: adjusted as in Table 3 including plurality) [13].

Table 3 Effects of infertility diagnosis with and without ART treatment on adverse child outcomes

Diagnosis	ART	AOR (95 % CI)[a]	
		Premature birth	Low birthweight
Fertile	No	1.00 (reference)	1.00 (reference)
Male factor	Yes	*1.24* (*1.07*, *1.44*)	*1.27* (*1.08*, *1.48*)
Endometriosis	Yes	1.22 (0.90, 1.66)	0.97 (0.70, 1.33)
Endometriosis	No	*1.66* (*1.26*, *2.18*)	*1.46* (*1.07*, *1.99*)
Ovulation disorders	Yes	*1.93* (*1.55*, *2.41*)	*1.60* (*1.23*, *2.06*)
Ovulation disorders	No	*1.38* (*1.10*, *1.74*)	*1.38* (*1.09*, *1.76*)
Tubal factors	Yes	*1.47* (*1.16*, *1.85*)	*1.42* (*1.11*, *1.82*)
Reproductive inflammation[b]	No	*1.44* (*1.27*, *1.65*)	*1.54* (*1.34*, *1.76*)

Adapted from [14]; italicized values are significant; data from 2004–2008

[a] Models adjusted for maternal age, race and ethnicity, education, preexisting medical conditions (chronic hypertension and diabetes mellitus), and plurality at birth

[b] Includes inflammatory conditions of the fallopian tubes, uterus, and peritoneal cavity

When examining child outcomes through age three, specifically the likelihood of enrollment in Early Intervention (EI) programs, a proxy for risk of developmental delays, children born from ART were more likely than spontaneously conceived children to be enrolled, and preterm birth was not the primary contributor through which ART was associated with EI enrollment. Similarly, higher EI rates were observed among children born to mothers with subfertility indicators [27].

Table 2 Risks of adverse child outcomes by fertility group and plurality

Plurality	Fertility group	AOR (95 % CI)[a]			
		Preterm	Low birthweight	Small for gestation	Perinatal death
Singletons	Fertile	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Subfertile, no ART	*1.24* (*1.12*, *1.38*)	*1.20* (*1.06*, *1.36*)	0.95 (0.85, 1.06)	*1.51* (*1.05*, *2.17*)
	ART	*1.53* (*1.40*, *1.67*)	*1.51* (*1.37*, *1.67*)	1.05 (0.96, 1.16)	1.00 (0.67, 1.50)
	Fertile	*0.80* (*0.72*, *0.89*)	*0.83* (*0.74*, *0.94*)	1.05 (0.94, 1.17)	*0.66* (*0.46*, *0.95*)
	Subfertile, no ART	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	ART	*1.23* (*1.08*, *1.41*)	*1.26* (*1.08*, *1.47*)	1.10 (0.96, 1.27)	0.66 (0.40, 1.11)
Twins	Fertile	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Subfertile, no ART	1.35 (0.57, 3.20)	1.01 (0.85, 1.20)	*0.80* (*0.66*, *0.98*)	*3.73* (*2.37*, *5.87*)
	ART	0.89 (0.68, 1.18)	0.98 (0.89, 1.09)	*0.85* (*0.75*, *0.96*)	*0.55* (*0.34*, *0.89*)
	Fertile	0.74 (0.31, 1.76)	0.99 (0.83, 1.18)	*1.25* (*1.02*, *1.52*)	*0.27* (*0.17*, *0.42*)
	Subfertile, no ART	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	ART	0.66 (0.23, 1.90)	0.98 (0.82, 1.17)	1.06 (0.86, 1.30)	*0.15* (*0.09*, *0.25*)

Adapted from [26]; italicized values are significant; data from 2004–2008

[a] Models adjusted for maternal age, race and ethnicity, marital status, education, smoking, prenatal care, parity, chronic and pregnancy-induced hypertension, other fertility-related conditions, and infant gender

Table 4 Risks of maternal adverse outcomes among ART-treated study cohort by diagnosis

Diagnosis	AOR (95 % CI)[a]		
	Pregnancy hypertension	Gestational diabetes	Prenatal admissions
Male factor only	1.00 (reference)	1.00 (reference)	1.00 (reference)
Endometriosis	*0.61* (*0.41*, *0.89*)	0.79 (0.49, 1.26)	*1.79* (*1.20*, *2.68*)
Ovulation disorders	0.98 (0.74, 1.30)	*1.77* (*1.28*, *2.45*)	*2.01* (*1.44*, *2.80*)
Diminished ovarian reserve	1.30 (0.92, 1.83)	0.85 (0.54, 1.34)	1.42 (0.89, 2.27)
Tubal factors	0.74 (0.55, 1.01)	1.19 (0.84, 1.69)	*1.49* (*1.04*, *2.13*)
Uterine factors	0.55 (0.26, 1.18)	1.51 (0.77, 2.97)	*2.68* (*1.40*, *5.15*)
Other factors	0.93 (0.72, 1.21)	0.88 (0.63, 1.23)	*1.66* (*1.21*, *2.29*)

Adapted from [13]; italicized values are significant; data from 2004–2008

[a] Models adjusted for maternal and paternal ages, race, and ethnicity, education; maternal preexisting conditions (chronic hypertension and diabetes mellitus); semen source; oocyte source; micromanipulation; embryo state; number of embryos transferred; and plurality

Maternal health outcomes

Within the study cohort of women treated with ART, we evaluated the effect of infertility diagnoses on perinatal outcomes, with pregnancies affected by male factor only as the reference group [13]. Significantly increased risks included gestational diabetes, prenatal hospital admissions, and primary cesarean section (uterine factors, AOR 1.96, 95 % CI 1.15, 3.36) (Table 4).

When we examined pregnancy and birth outcomes by infertility-related diagnoses with and without ART treatment, and compared them to outcomes among fertile women, most women with infertility-related diagnoses experienced significantly higher risks for pregnancy hypertension, gestational diabetes, and prenatal admissions ([14]; Table 5). We also compared postpartum rehospitalization rates among subfertile women with and without ART treatment and fertile women [28]. We did not find a significantly higher risk for subfertile women treated with ART either in the first 6 weeks postpartum or up to 1 year after birth. These findings add further support for the primary role of diagnosis—rather than treatment—in the risk for adverse maternal-child outcomes among families with infertility.

Clinical implications

It is well known that multiple pregnancy is the major risk factor in ART. National guidelines issued by the Society for Assisted Reproductive Technology on the number of embryos to transfer (first in 1998 and revised downward in 1999, 2004, 2006, 2008, 2009, 2013) have helped dramatically reduce the rates of multiple pregnancy after ART [29]. The triplet and higher-order multiple birth rate rose by more than 400 % from 1980 to 1998 but has trended downward since, with average annual declines of more than 4 % since 2004 [30]. Our studies show that the focus on single embryo transfer is important and must continue since not only multiple birth but also multiple gestation and multiple embryo transfer can affect outcome even in singleton births. SART has recently encouraged practitioners and patients to focus on cumulative delivery rates

Table 5 Effects of infertility diagnosis with and without art treatment on adverse maternal outcomes

Diagnosis	ART	AORs (95 % CI)[a]		
		Pregnancy hypertension	Gestational diabetes	Prenatal admissions
Fertile	No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male factor	Yes	*1.42* (*1.23*, *1.63*)	1.15 (0.96, 1.38)	1.18 (0.97, 1.43)
Endometriosis	Yes	0.90 (0.64, 1.26)	0.93 (0.62, 1.39)	*1.97* (*1.38*, *2.80*)
Endometriosis	No	1.24 (0.94, 1.63)	1.08 (0.75, 1.57)	*3.34* (*2.59*, *4.31*)
Ovulation disorders	Yes	*1.53* (*1.23*, *1.91*)	*2.17* (*1.72*, *2.73*)	*2.31* (*1.81*, *2.96*)
Ovulation disorders	No	1.09 (0.83, 1.42)	*1.94* (*1.52*, *2.48*)	*2.56* (*2.05*, *3.21*)
Tubal factors	Yes	1.08 (0.84, 1.38)	*1.42* (*1.09*, *1.84*)	*1.51* (*1.14*, *2.01*)
Inflammation	No	0.98 (0.84, 1.14)	0.88 (0.73, 1.06)	*2.79* (*2.47*, *3.15*)

Adapted from [14]; italicized values are significant; data from 2004–2008

[a] Models adjusted for maternal age, race and ethnicity, education, preexisting medical conditions (chronic hypertension and diabetes mellitus), and plurality at birth

(rather than outcomes after a single cycle) with the transfer of fewer embryos over more cycles, also potentially reducing the rate of multiple births from ART [31].

The observation that underlying subfertility and infertility-related diagnoses are important factors in both maternal and child morbidity may ultimately have direct implications for clinical care; however, given the preliminary nature of this research, it is premature to make specific clinical recommendations. What is clear is that informed consent for ART should include some discussion of the potential for infertility diagnosis to affect obstetric outcomes. Data so far suggest that management of pregnancies for patients with differing diagnoses should differ with, for example, greater attention to hypertension in patients with tubal disease and greater attention to both hypertension and gestational diabetes in patients who have ovulatory disorders. More importantly, the clinical course related to underlying subfertility should be considered during ART cycle management when decisions are made with regard to amount of medication used and advisability of transferring multiple embryos. Realization that some poor prognosis patients may have a poor obstetric course advises that a balance be reached between achieving pregnancy and obtaining an optimal result for mother and child.

Changing the research focus

Our findings suggest a need to change the research focus from a primary emphasis on ART treatment to a greater scrutiny of the contribution of preexisting pathology underlying infertility on health outcomes for mothers and children. At present, the most widely cited measure of subfertility is based on mothers' description in surveys of how long they have been trying to become pregnant, but this approach is subject to recall bias, may lack specificity in quantifying treatment parameters [32], and is not a routine data item in health service or vital statistics databases. In addition, this information fails to include the wide range of different causes for the subfertility and fails to include the underlying medical conditions which are important to understanding the effects on outcome. Developing means to collect subfertility information will be an important future direction for infertility research. Further, it is essential that we develop methods for longitudinal linkage of subfertility clinical data with population databases, such as is being spearheaded by CDC in several states in the USA [33–36]. As linkages between systems add breadth and a longitudinal dimension to outcome assessment, the potential for more sophisticated analyses that can separate the effects of ART from the underlying infertility-related diagnoses are possible but commitment from research funders and policymakers will be necessary to take advantage of the power of these research platforms.

Conclusion

The challenges of dealing with infertility will undoubtedly continue. By shifting the emphasis of the research agenda from the effects of a single intervention—the in vitro fertilization and assisted reproductive technologies—to the nature and consequences of infertility, we can better refine clinical solutions to this ongoing challenge.

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