Published in final edited form as:

Paediatr Perinat Epidemiol. 2014 May ; 28(3): 191–202. doi:10.1111/ppe.12121.

Methodology for Establishing a Population-Based Birth Cohort Focusing on Couple Fertility and Children's Development, the Upstate KIDS Study

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Abstract

Background—Critical data gaps remain regarding infertility treatment and child development. We assessed the utility of a birth certificate registry for developing a population cohort aimed at answering such questions.

Methods—We utilized the Upstate New York live birth registry (N=201,063) to select births conceived with (n=4,024) infertility treatment or exposed infants, who were then frequency-matched by residence and plurality to a random sample of infants conceived without (n=14,455) treatment or unexposed infants, 2008–2010. Mothers were recruited at 2–4 months postpartum and queried about their reproductive histories including infertility treatment for comparison with birth certificate data. Overall, 1,297 (32%) mothers of exposed and 3,692 of unexposed (26%) infants enrolled.

Results—Twins represented 22% of each infant group. The percentage of infants conceived with/without infertility treatment was similar whether derived from the birth registry or maternal report: 71% none, 16% drugs or intrauterine insemination, and 14% ART. Concordant reporting between the two data sources was 93% for no treatment, 88% for ART and 83% for fertility drugs, but differed by plurality. Exposed infants had slightly ($p<0.01$) earlier gestations than unexposed

infants (38.3 ± 2.8 and 38.7 ± 2.7 weeks, respectively) based upon birth certificates but not maternal report (38.7 ± 2.7 and 38.7 ± 2.9 , respectively). Conversely, mean birthweight was comparable using birth certificates (3157 ± 704 and 3194 ± 679 grams, respectively), but differed using maternal report (3167 ± 692 and 3224 ± 661 , respectively) $p < 0.05$.

Conclusions—The birth certificate registry is a suitable sampling framework as measured by concordance with maternally reported infertility treatment. Future efforts should address the impact of factors associated with discordant reporting on research findings.

An evolving literature has developed during the past two decades focusing on the relation between infertility treatment and children's health. Results from quantitative reviews suggest that singleton children conceived with assisted reproductive technologies (ART), or treatments involving the handling of gametes outside the body, have shorter gestations, reduced birth size and a greater odds of birth defects in comparison to children conceived without such treatment.^{1–4} Similar findings have been reported for twins.^{5–7}

To date, few data exist regarding the long term health status of children conceived with various infertility treatments,⁸ particularly sufficiently sized prospective cohort studies that are suitable for following children's varying developmental trajectories.⁹ These data gaps persist despite emerging evidence suggesting that ART conceived children might have more adverse health and developmental outcomes in comparison to children conceived without such treatment as recently reviewed,^{10–12} and the increasing percentage of ART conceived births in the United States ($\approx 1.4\%$) and elsewhere.¹³ Moreover, utilization of IVF in the United States is estimated to be below the level of demand, possibly a function of socioeconomic disparities such as lower educational attainments, lack of insurance coverage, and residence in non-urban environments among infertile couples who do not seek treatment.¹⁴

Another lingering data gap is an uncertain causal model for assessing infertility treatment and children's health status in that affected parents may have suboptimal fecundity, which is defined as the biologic capacity of men and women for reproduction.¹⁵ For example, some evidence suggests that women requiring a longer time-to-pregnancy (TTP) are at increased risk for adverse pregnancy outcomes such as preterm delivery or low birth weight.^{16–18} However, this body of research relies upon pregnant women and self reported TTP, which has been shown to have low validity and bi-directional reporting errors when compared to the gold standard or prospective cohort studies with preconception enrollment but adequate for differentiating infertile couples at $TTP > 12$ months.¹⁹ Still other population level data suggest that women who become pregnant after 13+ months of trying without treatment have pregnancy outcomes that more closely resemble those of women requiring less time than couples undergoing ART.²⁰ The inability to design trials where ART and infertility treatment would be randomized to fecund couples precludes our complete understanding of the relation between fecundity, related impairments and infant and child health outcomes. To this end, creative approaches for assessing this question are needed.^{21,22}

We designed The Upstate New York Infant Development Screening Program, or Upstate KIDS, to address couple fecundity and the use of a spectrum of infertility treatments in relation to children's growth and development through three years of age. A secondary goal

of Upstate KIDS is to assess the American Academy of Pediatrics' (AAP) algorithm for screening children's development and the need for early intervention.^{23,24} This paper provides an overview of the study design and methodology utilized by the Upstate KIDS Study, particularly focusing on the utility and feasibility of the birth certificate registry as a sampling framework for assessing fecundity and its impairments and children's health status. As such, this paper empirically evaluates concordance between birth certificate and maternally reported infertility treatment data. Further, we assess whether gestation and birthweight vary by exposure status and data source to evaluate the suitability of birth certificate registries for establishing cohorts for long-term follow-up.

Methods

Study design and population

The referent population for Upstate KIDS comprised all live births to Upstate New York resident mothers who delivered between July 2008 and May 2010, as captured in the State's electronic Perinatal Data System (N=201,063). Upstate New York comprises 57 counties excluding the five New York City boroughs, and was selected as the referent population given its early inclusion of infertility treatment on birth certificates in 1996.²⁵ Live births were sampled for geographic representation by the State's seven Regional Perinatal Networks and by plurality of birth (singleton or twin) using recruitment targets generated from the 2005–2007 live birth registries. This population based sampling strategy framework enables the estimation of sampling weights that can be applied for generalization to the State level.

A matched exposure cohort design was utilized. Specifically, infants whose birth certificates noted the use of infertility treatment were conceptualized as 'exposed' infants (n=4,024) and subsequently frequency-matched on maternal geographic residence and plurality of birth at a ratio of $\approx 1:3$ to 'unexposed' infants, or those without any notation of infertility treatment (n=14,555). For twin pregnancies, one infant was randomly selected for inclusion in the primary cohort. However, the twin sibling of the index child was included in a secondary cohort so that mothers were able to report on both infants. Another cohort also included all higher order births (n=126 triplets, n=8 quadruplets) and was followed similarly to the primary cohort to answer more specific questions pertaining to multiples in subsequent publications. This paper focuses on the primary cohort only.

Following establishment of the primary cohort by the New York State Department of Health, the recruitment process commenced in September 2008 and continued through December 2010 with the mass mailing of introductory letters and study brochures to the targeted study population (n=18,479), whose infants were approximately 2–4 months of age by September 2008. Introductory letters stated that the Study was interested in women's pregnancy histories along with childhood growth and development during the first three years of life. Approximately two weeks after each monthly mailing, follow-up telephone calls were undertaken to screen for eligibility: mother's residence at birth and enrollment within the specified catchment area; ability to communicate in English or Spanish; and the index infant or its twin was currently alive. Interested mothers were sent a study packet, as were all mothers for whom no telephone contact could be made after a maximum of four

attempts. Periodic postcard reminders and Facebook® or email messages were used to encourage the return of data collection instruments within the study timeframe for each developmental assessment. Telephone reminder calls were placed if study data collection instruments were outstanding 10 days. All materials were offered in English and Spanish. Enrollment was defined as receipt of signed parental consent.

Data and biospecimen collection

Upon enrollment of the infant, a packet of questionnaires was sent to the mother for completion. The maternal baseline questionnaire captured information about her medical and reproductive history, behaviors while pregnant with the index infant and sociodemographic characteristics. Mothers were specifically queried about all medical procedures undertaken to help conceive the index birth. Various options were provided for the following question, and mothers were instructed to check all that applied. No definitions were provided for treatment options beyond formal names and acronyms, though examples of medications were listed.

What medical services or medications did you receive in the cycle that you became pregnant with this pregnancy?—ART-specific options included: *in vitro* fertilization with or without intracytoplasmic sperm injection (ICSI) and/or the use of donor eggs or sperm; frozen embryo transfer (FET); gamete intrafallopian transfer (GIFT); zygote intrafallopian transfer (ZIFT); and assisted hatching. Fertility drugs options included: tablet medications (e.g., Clomid®, Serophene®); injectable medications to trigger ovulation (e.g., Ovidrel®, Profasi®, Pregnyl®, Novarel®); injectable follicular stimulation medications (e.g., Repronex®, Follistim®, Gonal-F®, Menopur®); or other medications to help with conception (e.g., Metformin®, Provera®, Lupron®).

A baseline questionnaire was completed for each infant enrolled in the study to provide information on newborn characteristics including gestational age and birth size at delivery, feeding practices and health status. While beyond the scope of this initial baseline paper, other data collection instruments utilized in the Study included the *Ages & Stages Questionnaires*® for screening parental rating of children's development at 8, 12, 18, 24, 30, and 36 months of age^{26–28} and the 23-item Modified Checklist for Autism in Toddlers (M-CHAT) at 18 and 24 months.²⁹ The ASQ is an established valid parental rating instrument written at the 4th to 6th grade reading level, and comprises 30-items representing five developmental areas (i.e., communication, gross and fine motor, personal-social, and problem solving).³⁰ Parents also maintained a Child Health Journal for capturing items such as growth and development. Remuneration was minimal (\$30 for return of all baseline instruments), along with periodic tokens of appreciation. All data collection instruments utilized TeleForm® (Verity, Inc. Pleasanton, CA) formatting for optical scanning and data entry. Several initiatives were undertaken to maintain retention in the study including family support specialists who engaged families and served as liaisons with the study and with the Early Intervention Program for New York State. Full human subjects' approval was obtained from all participating institutions (NYSDOH IRB #07-097; UAlbany #08-179), and informed consent was given prior to data collection.

Operational definitions

Maternal sociodemographic characteristics were assessed in relation to the concordance of infertility treatment as captured on birth certificates and maternal report, largely given the socioeconomic disparity in seeking care. These included: age, body mass index (BMI, weight in kg/height in m²), education, health insurance, marital status, and race/ethnicity. Gravidity and parity were defined by maternal report as the number of prior pregnancies and live births, respectively. For analysis, we dichotomized parity as primipara or 0 versus multipara or 1+ prior viable pregnancy.

Infertility treatment was defined by birth certificates and maternal report. Specifically, any notation that the pregnancy resulted from infertility treatment on birth certificates irrespective of type denoted exposure status for the infant. Infants born following any of the following treatments as listed on birth certificates as abstracted from medical records were considered exposed, while infants without such checkmarks were considered unexposed. The data field appears as follows:

- ☐ Pregnancy resulted from infertility treatment (if yes, check all that apply)
 - ☐ Fertility-enhancing drugs, artificial or intrauterine insemination
 - ☐ Assisted reproductive technology (e.g., IVF, GIFT)

Infertility treatment was also defined by maternal report of having conceived the index pregnancy with medication, insemination and/or ART procedures.

Infant outcomes relevant to the question of treatment (exposure) included gestational age as measured by clinical estimates and from the last menstrual period (LMP) and birth weight converted to grams from pounds/ounces. We assessed both outcomes based upon the birth certificates and also as reported by mothers.

Statistical analysis

We fully inspected all data for completeness and valid ranges, and by measures of central tendency and variation for continuous data. Differences in participant characteristics based on birth certificate data were compared by participation and exposure status using t-tests for means and chi-square for differences in proportions. Concordance for infertility treatment between the two data sources was assessed in three ways: 1) no infertility treatment; 2) yes, irrespective of treatment type; and 3) yes, for a specific type of treatment such as ART or fertility drugs. Concordance also was estimated as the percentage of agreement between data sources for no, any or specific type(s) of treatment. For exploration purposes and in full recognition of the absence of a gold standard in our study, we estimated sensitivity and specificity for the infertility classification based on birth certificate while using maternal report as “gold standard”. This was achieved by accounting for the sampling framework and using Bayes formula³¹ as follows:

$$\text{Sensitivity} = \text{PPV} * \text{P}(\text{infertility based on birth certificate}) / ((1 - \text{NPV}) * (1 - \text{P}(\text{of infertility in birth certificate})) + \text{PPV} * (\text{P}(\text{infertility based on birth certificate}))) \text{ and}$$

$$\text{Specificity} = \text{NPV} * (1 - \text{P}(\text{infertility based on birth certificates})) / ((1 - \text{PPV}) * \text{P}(\text{infertility in birth certificates})) + (1 - \text{NPV}) * (1 - \text{P}(\text{infertility in birth certificate})))$$

We estimated gestational age and birthweight by infertility treatment exposure status based upon maternal report, and also as reported on the birth certificate and compared the distributions. This analysis permitted us to evaluate whether ascertainment mode (i.e., birth certificate or maternal report) for categorizing exposure status or infertility treatment yielded similar distributions for gestation and birthweight. We did not implement multivariable analyses, given that the focus of this paper is in assessing concordance of the sampling frameworks for identifying infertility treatment and the two perinatal outcomes (gestation and birthweight) and not etiology, *per se*, which will be the subject of future work. Significance was assessed using either the Chi-square for categorical or the t-test statistic for continuous data.

Results

Table 1 compares sociodemographic characteristics by both participation and exposure status. Participants were significantly more likely to be white, older, more educated, have fewer live births, have private health insurance in comparison to nonparticipants, and to reside in Rochester, Syracuse and New York City affiliated areas. However, many of the observed differences reflected very minor differences between groups irrespective of statistical significance. Some of these differences may have also been due to the slightly higher response rate of those who were exposed to infertility treatment, as these same differences also were seen by exposure status for both nonparticipants and participants. Holding exposure status constant, exposed participants were similar to exposed non-participants in all characteristics except for race, education and region. Among nonparticipants, a slightly higher percentage of twins were conceived with infertility treatment than without (i.e., 24.0% and 20.7%, respectively). This pattern was not observed among participants.

Table 1 also reflects that the study cohort comprises 1,297 (26%) infants conceived with and 3,692 (74%) infants without treatment as based on the birth certificate, reflecting overall participation rates of 32% (1,297/4,024) and 26% (3,692/14,455), respectively. Singleton pregnancies comprised $\approx 78\%$ of each group of infants, while twins comprised $\approx 22\%$. Comparable recruitment rates for exposed and unexposed infants were obtained across perinatal sampling regions, though the small differences achieved significance.

As Table 2 reflects, the distribution of infants conceived without/with infertility treatment as derived from the birth certificate registry was 74% for no treatment, 12% for drugs or intrauterine insemination only (IUI), 13% for ART, and 1% for unspecified treatment. When based upon maternal report, this distribution was 71% for none, 16% for drugs/IUI only, and 14% for ART suggesting slightly higher reporting for infertility treatment by mothers in comparison to birth certificate data. The overall concordance irrespective of treatment type between the two data sources was 90%, increasing to 92% when categorizing infertility treatment as any versus none. Of note is that a comparable ($\approx 13\%$) percentage of mothers reporting having conceived with fertility drugs with/without IUI or ART. As for the latter subgroup of mothers, 18% reported receiving ART with donor gametes and 28% with assisted hatching techniques (data not shown). The overall kappa statistic between maternal report and birth certificates for use or not of infertility treatment is 80.7%.

Estimated sensitivity and specificity for the overall cohort, again assuming maternal report to the gold standard, were 0.55 and 0.99, respectively. When restricting the analysis to singletons, the estimates were 0.56 and 0.99, respectively, and 0.74 and 0.97, respectively, for twins.

Table 3 reflects that concordance varied when stratifying the analysis by treatment exposure status among the 4,843 (97%) mothers who completed the baseline questionnaire. Specifically, concordance was 97% for no treatment, 81% for any treatment, and 73% for a specific type of treatment defined as either ART or fertility drugs. Concordant reporting varied significantly by college education and plurality of birth for all categories of infertility treatment, while other characteristics were treatment type specific. Discordant reporting for any or ART treatment was associated with younger age, higher BMI, nonwhite self identified race, less than a college education, unmarried, and multiple births; however, most absolute differences were small despite statistical significance.

With regard to pregnancy outcomes, gestational age but not birthweight distributions significantly varied by exposure status when using birth certificate data, whereas the reverse was true when based upon maternal report albeit with small observed differences (Table 4). Specifically, infants conceived with versus without treatment had shorter mean gestations (37.9 ± 2.6 and 38.1 ± 2.4 weeks) based upon clinical estimates as reported on birth certificates, and also when estimated by LMP though with a smaller observed difference (38.3 ± 2.8 and 38.7 ± 2.7 weeks, respectively). Comparable mean gestations were observed irrespective of infertility treatment when based upon maternal report (38.7 ± 2.7 and 38.7 ± 2.9 weeks, respectively). However, it is important to note that 34% of mothers did not provide a LMP. We also asked mothers to report their “length of gestation”, which we did not define. Again, we observed no significant difference in gestation by exposure status (38.0 ± 2.8 and 38.2 ± 2.7 weeks, respectively). Conversely, mean birthweights were comparable for infants conceived with/without treatment based upon birth certificate data ($3,157 \pm 704$ and $3,194 \pm 679$ grams, respectively), but significantly different when based upon maternal report ($3,167 \pm 692$ and $3,224 \pm 661$ grams, respectively). Of note, similar results were observed even when restricting the analysis to singleton births, most likely reflecting a comparable percentage (22%) of twins in both the exposed and unexposed cohorts. One difference was observed, however. Specifically, exposed singletons were 54-grams ($P < 0.05$) lighter than unexposed infants when based upon birth certificate exposure status (data not shown).

Comments

To our knowledge, the Upstate KIDS Study is the first U.S. attempt to develop a population-based cohort with the explicit purpose of assessing impaired fecundity, infertility treatment and children’s health through 3 years of age. Our findings illustrate the utility and feasibility of using the New York State Live Birth Certificate registry for designing a matched exposure cohort study suitable for longitudinal data collection and follow up of children from birth through early childhood. Concordance was high (>90%) for the capture of infertility treatment on birth certificates in comparison to maternal report at approximately four months postpartum even when considering type of treatment, though it became lower

when assessing specific types of treatment such as ART or fertility drugs. Upon further inspection of discordancy for type of infertility treatment, most arose from underreporting on the birth certificate in comparison to maternal report (7% of birth certificates were missing ART/fertility drugs versus 3% of maternal reports). Overall, this finding suggests that women are accurately reporting treatment for the index birth rather than for past births, given an earlier report that suggested mothers may misreport past ART treatment when queried after birth.³²

The reliability of the birth certificate for identifying infants conceived with infertility treatment in relation to maternal report is reassuring in light of the limited reliability for various medical history type information on birth certificates, more generally.³³ An earlier validation study of infertility treatment in New York State randomly selected 440 birth certificates for comparison with maternity medical records.²⁵ The sensitivity, specificity, positive and negative predictive values of the *in vitro* fertilization checkbox on the certificate were 80%, 100%, 80%, and 100%, respectively. These sensitivity and specificity estimates are considerably higher than those we calculated for the Upstate KIDS Cohort after accounting for the sampling strategy, i.e., 55% and 99%, respectively. Sensitivity was higher for twins than singletons (74% and 56%, respectively), though specificity decreased slightly (97%) but only for twins. Our sensitivity and specificity estimates assuming maternal report as the gold standard were notably higher than a validation study conducted with Massachusetts 1997–2000 birth certificates, which linked with the gold standard of the National Assisted Reproductive Technologies Surveillance System.³⁴ Sensitivity was 24.3% for singletons, 31.8% for twins and 43.0% for triplets, with accompanying specificities of 99.8%, 95.6% and 66.2%, respectively). Of added note were findings from the Massachusetts validation study that the linkage failed to include 12% of live birth in the states reported to have occurred with ART or that 1.3% of twins had discrepant reporting on birth certificates. Reasons for the marked differences in sensitivities across studies remain unknown, but may reflect varying units of analysis (births versus ‘live birth delivery’ with multiples counted as 1 delivery), reporting or data capture differences of varying study periods.

Our findings pertaining the concordant reporting of infertility treatment are not directly comparable with past research, given the absence of similar sampling frameworks (e.g., postpartum women) and study designs (e.g., cross-sectional surveys) with one exception. Lynch and colleagues (2011) assessed the concordance of infertility treatment as captured by the Massachusetts birth certificate and maternal report for a targeted sample of 1,993 women.³⁵ Overall, study participation was 23% with no difference by infertility exposure status. Fully concordant reporting for infertility treatment was 53% for singletons and 23% for twins, and 37% and 63% for partial concordant reporting, respectively. However, no estimates of sensitivity or specificity were provided, likely given the absence of a gold standard. Similar to our study, Lynch and colleagues reported plurality of birth to be associated with discordant reporting but no sociodemographic characteristics other than age as observed in our study. However, we observed a much higher concordance in reporting including for specific types of treatment relative to theirs. While speculative, reasons for higher concordance may reflect differences in the comparison group or a later time period

for the Upstate KIDS Study (2008–2010) compared to the Massachusetts Study (2001) that fosters more conducive reporting of treatment by mothers.

Another possibility is that our findings may reflect specific guidance provided for obtaining infertility information for the revised 2003 birth certificate, since recent data assessing the 2003 birth certificate reported varying levels of sensitivity for data recorded on birth certificates relative to medical records.³⁶ Sensitivity was high for birthweight within 500 grams, cesarean delivery and cephalic presentation, but low for select items such as previous preterm birth and meconium staining. Another study compared birth certificate data with questionnaire data provided by pregnant women participating in the PIN Cohort Study and reported high agreement for demographics but lower agreement for gravid health.³⁷ Neither study, however, assessed the reliability of infertility treatment.

Other previous researchers have recognized the importance of establishing methods for addressing the many lingering questions about the impact of infertility treatment on children's health and well-being. Of note is the work by Schieve and colleagues (2007) who linked the U.S. ART surveillance system with the Massachusetts live birth-infant death registry, 1997–1998, given that Massachusetts was an early state to require insurance coverage for ART. ART was observed to be significantly associated with adverse pregnancy outcomes such as preterm delivery and low birthweight.⁴ Our results corroborate the earlier findings for gestation when using birth certificate data; however, maternal report did not corroborate the birthweight observation.

Continued efforts to delineate the causal ordering, if any, between couple fecundity, its impairments such as conception delay and infertility, the decision to seek treatment and specific types of treatment, and pregnancy and infant outcomes cannot be overstated for two key reasons. First, critical data gaps remain regarding this avenue of study. As such, we have few empirical data for well-defined populations that can be incorporated into clinical practice when informing couples about possible risks associated with specific treatment modalities. The second reason reflects the high prevalence of infertility in the U.S. and across the globe. While prevalence of infertility in the U.S. has been estimated at approximately 7% when relying on a construct measure³⁸ rather than via direct querying of individuals, its prevalence is reported to be considerably higher (16%) when utilizing novel methods such as the current duration approach.³⁹ Moreover with utilization of infertility services expected to increase, an increasing subgroup of children may be at risk for earlier deliveries and of smaller birth size and altered developmental trajectories in relation to children conceived without services. While the absolute number of children conceived with ART is small, underscoring the need for large population-based cohorts of sufficient size for detecting subtle differences that may be predictive about children's health across the lifespan, it is important to keep in mind the much larger percentage of children conceived with non-ART modalities such as ovulation stimulation with/without IUI. Schieve and colleagues (2009) addressed this important question and estimated that approximately 4.6% (95% CI 2.8%–7.1%) of U.S. infants were conceived with ovulation stimulation reflecting 4-times the ART contribution.⁴⁰ The estimated prevalence of ART or fertility drug usage in the referent Upstate New York Cohort was 1%, which increased to 12% in the study cohort reflecting our sampling on infants for whom infertility was checked on the birth certificate.

To this end, the prevalence of infants conceived with the help of infertility treatment, including specific subtypes, will vary. Our estimate of fertility drug usage is below that reported by mothers participating in the Pregnancy Risk Assessment Monitoring System for 2004–2005.⁴¹ Among the 10% of mothers reporting having sought infertility treatment, 29% reported using fertility drugs apart from ART possibly attributed to maternal reporting of usage for past and not just the index pregnancy.

In moving forward, sampling frameworks need to be developed to oversample subgroups of women who typically do not participate in research and/or to ensure population based sampling frameworks that allow weighting of findings to overcome such hurdles. Our findings further support the need for added attention to plurality of birth and other important sociodemographic factors observed to be associated with discordant reporting. Our overall estimated sensitivity of 55% for the Cohort needs to be cautiously interpreted, given the absence of a gold standard, and the observed differences in concordant reporting by important socio-demographic differences. Future work might benefit from additional linkages, if possible, with national ART registries. Unfortunately few options exist for linking study cohorts or samples for non-ART treatments, as no such registries exist. The characteristics of couples seeking infertility treatment very much resemble study participants in general and underscore the need for creative solutions for recruiting and retaining cohorts. This challenge is particularly important for geographic areas where health insurance plans may not cover infertility treatment.

Our response rate is low but in keeping with recent rates observed for other birth cohort studies. In fact, Nohr and colleagues 2006 assessed whether low participation rates introduce bias including for IVF and preterm birth.⁴² No bias was observed, though confidence intervals increased. Similar to research in general, we observed that our study cohort comprised more white, older, educated women with private health insurance. Moreover, these are some of the same characteristics associated with use of infertility and, more specifically, ART treatment even in countries with universal health insurance including coverage for ART.⁴³ The earlier work of Lynch and colleagues corroborated by our findings suggests that participants are more likely to be white, have a college degree or more, be married, aged 40 or older than nonparticipants. Reasons for the significant gestational age differences only when based upon birth certificates and not maternal report are unknown. Still, the magnitude of the reporting differences are small for both gestation (≈ 3 days) and birthweight (37 grams) and underscore the relevancy of this sampling framework for establishing birth cohorts. The higher mean birthweights for both groups of infants when based upon maternal report in comparison to birth certificates may suggest more favorable reporting by mothers for these two perinatal outcomes, conversion errors, or inaccurate birth certificate. However, such errors in reporting would have to be systematically lower for infants conceived with treatment than without. We know of no such data to support this explanation, though maternal recall of gestation and birthweight are reported to be good relative to the birth certificate,³⁷ and the birth certificate to be good relative to medical records.⁴⁴

In sum, birth certificate registries are reasonable sampling frameworks for establishing a cohort of infants to assess fecundity and its related impairments and treatment in relation to

children's growth and development across sensitive windows of childhood and beyond. Efforts to link with available treatment registries are encouraged along with novel strategies for validating non-ART treatment. Sampling strategies that oversample on maternal sociodemographic characteristics may be needed to minimize underrepresentation of younger, less educated, unmarried, and parous women, or to allow for the application of population derived weights for such adjustment.

Acknowledgements

Funded by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (contracts HHSN267200700019C; HHSN275201200005C). The authors thank Kira Leishear and Patricia Moyer for their statistical programming assistance, and John Piddock and Larry Schoen for their assistance with vital registries.

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Table 1

Sociodemographic comparison by participation and exposure status, Upstate KIDS Study.

Characteristic	Nonparticipants (N=13,490) ^a		Participants (N=4,989)		P-values (comparing by)		
	Exposed (N=2,727) n (%)	Unexposed (N=10,763) n (%)	Exposed (N=1,297) n (%)	Unexposed (N=3,692) n (%)	Participation Status ^b	Exposure Status ^c - Nonparticipants	Exposure Status ^d - Participants
Maternal age (years):					<0.0001	<0.0001	<0.0001
<20	2 (0.1)	852 (7.9)	2 (0.2)	189 (5.1)			
20-29	494 (18.1)	5086 (47.3)	253 (19.5)	1718 (46.5)			
30-39	1800 (66.0)	4447 (41.3)	828 (63.8)	1661 (45.0)			
40	431 (15.8)	378 (3.5)	214 (16.5)	124 (3.4)			
Mean (SD)	34.2 (5.3)	28.4 (6.2)	34.1 (5.2)	29.1 (5.8)	<0.0001	<0.0001	<0.0001
Parity (# previous live births):					0.37	<0.0001	<0.0001
0, primipara	1586 (58.2)	4110 (38.2)	738 (56.9)	1405 (38.1)			
1, multipara	1141 (41.8)	6653 (61.8)	559 (43.1)	2287 (61.9)			
Mean (SD)	0.6 (0.8)	1.1 (1.3)	0.6 (0.9)	1.0 (1.2)	<0.0001	<0.0001	<0.0001
Plurality of index birth:					0.59	0.0002	0.74
Singleton	2072 (76.0)	8536 (79.3)	1011 (78.0)	2894 (78.4)			
Twin	655 (24.0)	2227 (20.7)	286 (22.0)	798 (21.6)			
Maternal race/ethnicity:					<0.0001	<0.0001	<0.0001
White, nonhispanic	2286 (83.8)	7015 (65.2)	1144 (88.2)	2952 (80.0)			
White, hispanic	94 (3.5)	1041 (9.7)	46 (3.6)	202 (5.5)			
Black, nonhispanic	87 (3.2)	1263 (11.7)	30 (2.3)	258 (7.0)			
Black, hispanic	3 (0.1)	58 (0.5)	0 (0.0)	12 (0.3)			
Other	257 (9.4)	1386 (12.9)	77 (5.9)	268 (7.3)			
Maternal educational attainment:					<0.0001	<0.0001	<0.0001
< high school	58 (2.1)	2037 (19.1)	13 (1.0)	318 (8.6)			
High school or equivalent	273 (10.1)	2528 (23.7)	74 (5.7)	676 (18.4)			
Some college	635 (23.4)	2914 (27.3)	254 (19.6)	1140 (31.0)			
College graduate	771 (28.4)	1637 (15.3)	382 (29.5)	733 (19.9)			

Characteristic	Nonparticipants (N=13,490) ^a		Participants (N=4,989)		P-values (comparing by)		
	Exposed (N=2,727) n (%)	Unexposed (N=10,763) n (%)	Exposed (N=1,297) n (%)	Unexposed (N=3,692) n (%)	Participation Status ^b	Exposure Status ^c - Nonparticipants	Exposure Status ^d - Participants
Graduate/professional school	980 (36.1)	1565 (14.7)	573 (44.2)	815 (22.1)			
Health insurance:					<0.0001	<0.0001	<0.0001
None	12 (0.4)	189 (1.8)	2 (0.2)	35 (1.0)			
Public	143 (5.2)	4157 (38.7)	59 (4.6)	1102 (29.9)			
Private	2535 (93.0)	6232 (58.0)	1224 (94.4)	2501 (67.8)			
Other	37 (1.4)	171 (1.6)	12 (0.9)	50 (1.4)			
Region					<0.0001	<0.0001	0.0002
Buffalo	336 (12.3)	1497 (13.9)	179 (13.8)	613 (16.6)			
Rochester	461 (16.9)	1436 (13.3)	129 (10.0)	363 (9.8)			
Syracuse	518 (19.0)	1807 (16.8)	146 (11.3)	382 (10.4)			
Albany	446 (16.4)	1858 (17.3)	274 (21.1)	771 (20.9)			
Westchester	371 (13.6)	1782 (16.6)	240 (18.5)	720 (19.5)			
Stony Brook	242 (8.9)	1112 (10.3)	171 (13.2)	514 (13.9)			
Nassau	134 (4.9)	429 (4.0)	70 (5.4)	102 (2.8)			
NYC-affiliated	215 (7.9)	831 (7.7)	82 (6.3)	222 (6.0)			
Unknown	4 (0.2)	11 (0.1)	6 (0.5)	5 (0.1)			

NOTE: All data are from that reported on birth certificates.

^aRepresents that targeted study population comprising all infants with the infertility treatment checked on birth certificates and 3 matched comparison infants.

^bComparison of non-participants (columns 1 and 2) with participants (columns 3 and 4).

^cComparison of exposed and unexposed within non-participants (columns 1 and 2).

^dComparison of exposed and unexposed within participants (columns 3 and 4).

Table 2

Concordance of infertility treatment between birth certificates and maternal report, Upstate KIDS (n=4,843).

Birth Certificate	Maternal Report			
	No treatment n (%)	Fertility drugs n (%)	ART n (%)	Total n (%)
No treatment	3,311 (93)	183 (5)	85 (2)	3,579 (74)
Fertility drugs	62 (10)	504 (83)	38 (6)	604 (12)
ART	22 (4)	51 (8)	537 (88)	610 (13)
Other ^a	24 (48)	13 (26)	13 (26)	50 (1)
Total	3,419 (71)	751 (16)	673 (14)	4,843 (100)

NOTE: All percentages were rounded.

^a Other denotes birth certificates that had a check mark for infertility treatment but did not specify whether it was fertility drugs or ART.

Table 3

Select maternal characteristics by concordance of reporting infertility treatment between birth certificate and maternal report and type of infertility treatment, Upstate KIDS (n=4,843).

Characteristic	Concordant n %	Discordant n %
<i>No infertility treatment as reported by mother (n=3,419) ^a</i>	(n=3,311; 97%)	(n=108; 3%)
Private health insurance (yes) ^{**}	2171 (66)	89 (82)
Race (white)	2831 (86)	95 (88)
Index birth is mother's first birth (yes)	961 (29)	33 (31)
College education (yes) ^{**}	1327 (40)	63 (59)
Married or living as married (yes)	2775 (85)	94 (89)
Plurality: [*]		
Singleton	2707 (82)	97 (90)
Twins	604 (18)	11 (10)
	Mean (±SD)	
Maternal age ^{**}	28.8 (±5.8)	31.8 (±5.4)
Pre-pregnancy BMI	27.0 (±6.8)	27.2 (±7.6)
<i>Yes, any infertility treatment as reported by mother (n=1,424) ^b</i>	(n=1,156; 81%)	(n=268; 19%)
Private health insurance (yes) [*]	1104 (96)	247 (93)
Race (white) [*]	1070 (93)	236 (88)
Index birth is mother's first birth (yes) [*]	471 (41)	90 (34)
College education (yes) ^{**}	868 (75)	170 (63)
Married or living as married (yes) [*]	1094 (96)	242 (93)
Plurality: ^{**}		
Singleton	891 (77)	112 (42)
Twins	265 (23)	156 (58)
	Mean (±SD)	
Maternal age ^{**}	34.3 (±5.1)	33.0 (±4.8)
Pre-pregnancy BMI [*]	27.1 (±6.8)	28.2 (±7.0)
<i>Yes, infertility treatment (specifically drugs or ART) as reported by mother (n=1,424) ^c</i>	(n=1,041; 73%)	(n=383; 27%)^c
Private health insurance (yes)	993 (95)	358 (94)
Race (white) ^{**}	968 (93)	338 (88)
Index birth is mother's first birth (yes)	422 (41)	139 (36)
College education (yes) ^{**}	781 (75)	257 (67)
Married or living as married (yes) ^{**}	995 (97)	341 (92)
Plurality: ^{**}		
Singleton	810 (78)	193 (50)

Characteristic	Concordant n %	Discordant n %
Twins	231 (22)	190 (50)
	Mean ($\pm$ SD)	
Maternal age	34.2 ($\pm$ 5.2)	33.6 ($\pm$ 4.9)
Pre-pregnancy BMI [*]	27.0 ($\pm$ 6.8)	28.0 ($\pm$ 7.1)

NOTE: Characteristics as noted on birth certificates except for maternally reported marital status, which is not on the birth certificate.

^{*} P <0.05;

^{**} P <0.01

^a Among women who self-reported no infertility treatment by questionnaire. Discordant reporting denotes a check box response for having had infertility treatment on birth certificates.

^b Among women who self-reported any infertility treatment. Discordant reporting denotes no exposure to any infertility treatment on the birth certificate, which does not match the maternal report.

^c Among women who self-reported a specific type (ART or fertility drugs) of infertility treatment. Discordant reporting denotes no exposure to a specific type of infertility treatment (i.e., fertility drugs or ART) on the birth certificate, which does not match the maternal report.

Table 4

Infant outcomes by source of reporting and infertility treatment exposure status, Upstate KIDS (n=4,843).

Infant Outcome	Based Upon Birth Certificates				Based Upon Maternal Report			
	Exposed (n=1,264)		Unexposed (n=3,579)		Exposed (n=1,264)		Unexposed (n=3,579)	
	n	%	n	%	n	%	n	%
Gestation – clinical estimate (weeks) ^a				*				
<28	18	1.4	42	1.2	--	--	--	--
29–32	39	3.1	84	2.4	--	--	--	--
33–36	202	16.0	465	13.0	--	--	--	--
37–39	691	54.7	2003	56.0	--	--	--	--
40–41	308	24.4	975	27.2	--	--	--	--
42	6	0.5	10	0.3	--	--	--	--
Mean (±SD)	37.9	(2.6)	38.1	(2.4)**	--	--	--	--
Gestation – LMP estimate (weeks) ^b				**				
<28	15	1.3	31	0.9	7	0.9	25	1.1
29–32	43	3.7	88	2.6	25	3.1	77	3.2
33–36	211	17.9	470	13.9	120	14.8	353	14.8
37–39	600	50.9	1727	51.0	403	49.6	1126	47.2
40–41	275	23.3	896	26.5	213	26.2	627	26.3
42	35	3.0	175	5.2	44	5.4	176	7.4
Mean (±SD)	38.3	(2.8)	38.7	(2.7)**	38.7	(2.7)	38.7	(2.9)
Birthweight (grams) ^c								*
<1500	37	2.9	75	2.1	28	2.5	67	2.1
1500–1999	40	3.2	130	3.6	34	3.0	86	2.7
2000–2499	125	9.9	301	8.4	118	10.4	235	7.5
2500–2999	251	19.9	666	18.6	220	19.5	589	18.7
3000–3499	401	31.7	1180	33.0	365	32.3	1044	33.2
3500–4000	300	23.7	921	25.7	269	23.8	852	27.1
4000	110	8.7	306	8.6	97	8.6	274	8.7

Infant Outcome	Based Upon Birth Certificates				Based Upon Maternal Report			
	Exposed (n=1,264)		Unexposed (n=3,579)		Exposed (n=1,264)		Unexposed (n=3,579)	
	n	%	n	%	n	%	n	%
Mean (±SD)	3156.6	(704.2)	3193.9	(678.7)	3166.8	(692.1)	3223.8	(660.5) [*]

NOTE: For mothers of twins, only data for the twin randomly assigned to the primary cohort was included for analysis. P-values correspond to tests of significance by exposure status for each birth characteristic within information source.

^{*} P<0.05;

^{**} P<0.01

^a Clinical estimate of gestational age in completed weeks as reported on the birth certificate.

^b Gestational age based on last menstrual period (LMP) rounded to nearest completed week. Note that 3,196 of 4,843 (66%) women provided a LMP on the baseline questionnaire, while 4,566 (94%) of women had a LMP listed on birth certificates.

^c Reported in grams or pounds/ounces on birth certificate and converted to grams. There are no missing data from the birth certificate. Birthweight was reported on the infant questionnaire as units of pounds and ounces and converted to grams. Note that 4,278 (88%) women reported birthweight on the infant questionnaire.