Maternal and Infant Characteristics among Users of Non-Assisted Reproductive Technology (non-ART) Infertility Treatments: Insights from the New 2003 Revision of Birth Certificate, Texas 2005-2006.
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It is widely recognized that assisted reproductive technologies (ART) such as in vitro fertilization (IVF), which has been used since the birth of the first "test tube baby" Louise Brown in 1978, has transformed the treatment of infertility and sub-fertility, allowing women and couples to overcome involuntary childlessness. ART methods refer to reproductive techniques used to achieve pregnancy by artificial or patially artificial means involving the handling of gametes and embryo outside the body. These technologies have long been known to elicit significant medical, reproductive and economic influences in developed countries (Hansen et al., 2005; Chambers et al. 2009) and increasingly beyond. Although their non-economic costs and consequences are often discussed, they have arguably not always been given due consideration. It is perhaps even less widely appreciated that a growing share of infants are born after non-ART fertility treatments, such as ovulation induction or controlled ovarian stimulation, and that these may also carry increased risks of multiple birth and concomitant sequelae and adverse outcomes, even among singleton births. Recent data for the U.S. indicate that over 1% of births are conceived with ART and that non-ART treatments are estimated to account for 4.6% of all U.S. births, or about four times greater that the ART contribution to the total U.S. birth cohort (Schieve et al. 2009).

Until recently, comprehensive U.S. data-sources recording non-assisted reproductive technology (ART) infertility treatments were very limited. This is despite the increasingly widespread use of such treatments and their established risks, which may include a higher incidence of multiple births and accompanying maternal and infant morbidity (Wang, 2002). A few studies have reported maternal, infant or other demographic characteristics among non-ART users in the U.S. using available sources of data such as the National Birth Defects Prevention Study and PRAMS, the Pregnancy Risk Assessment Monitoring System (Duwe, 2010; Lu, 2008). These data sources introduce potential sampling bias and other biases due to maternal self-reporting of exposure (including non-ART infertility treatments). Studies have also used large fertility-related databases (notably the National ART Surveillance System) that have often linked the collected data to vital records so as to obtain information on selected maternal, and almost all infant, outcomes (Schieve, 2007).

The present analysis makes innovative use of newly available birth certificate information that includes clinical data of interest to our purpose. Birth certificate data contain a wide range of reliable information for a very large number of live births on maternal socio-demographic (e.g. age, education, race/ethnicity, marital status) and infant characteristics (such as birthweight and the Apgar score, which is a useful clinical indicator for reporting overall status of the neonate and the need for, and response to, resuscitation efforts). The ability of birth certificate data to make available

methodologically rigorous and reliably collected information on select exposures and outcomes on a large number of mother-infant pairs makes it tremendously appealing to researchers for use in studies such as the one presented here.

The last revision of vital records was made in 2003, with full implementation in all states phased in over several years. In 2005, Texas implemented the new 2003 revision of the United States Standard Certificate of Live Birth (BC). Significantly, this includes the new data item: "Pregnancy resulted from infertility treatment." This is further categorized into ART births and ovulation induction / artificial insemination / intrauterine insemination (referred to here as non-ART infertility treatments). To date, no data on maternal and infant characteristics among non-ART treatment users have been reported using the 2003 BC revision, which provides population-based data for these treatments.

We examined all Texas live birth files for 2005-2006 to determine maternal characteristics, maternal co-morbidities and complications of pregnancy, labor and delivery, as well as infant characteristics and adverse infant outcomes among live births from non-ART use reported on BC data. Of the 799,857 live births recorded in Texas during 1/1/2005-12/31/2006, 795,599 were spontaneously conceived (SC) and 3,491 resulted from non-ART infertility treatments. In all, the records examined accounted for approximately 9% of all U.S. births recorded in the 2005-2006 period (the second highest total for any state after California). The study was institutional review board exempt.

Based on BC data, the incidence of live births from non-ART treatments was 0.5% of all live births in Texas and 4.5 times that of live births from ARTs during this period. Compared to the SC group, mothers in non-ART group were significantly older (36.1% were older than age 35 compared to 11.2% among the SC mothers) and were three times as likely to have a bachelor's or graduate degree. They were also significantly more likely to be White (85.7% vs. 75.8%) or Asian (6.5% vs. 3.5%), and to be privately insured (89.6% vs. 35.4%). They were also significantly less likely to be Hispanic (14.1% vs. 50.2%), or to use WIC food during pregnancy (8.0% vs. 52.4%). The non-ART mothers had a higher prevalence of chronic hypertension (3.0% vs. 1.0%) and chronic diabetes (0.9% vs. 0.6%), previous pre-term births and other previous adverse perinatal outcomes. In addition, they had a lower prevalence of smoking prior to (2.2% vs. 6.5%) or during pregnancy (1.2% vs. 5.9%).

We used multiple logistic regression to evaluate the effects of non-ART infertility treatments on several maternal and infant outcomes. A number of socio-demographic correlates were explored. The final set of models included controls for the following confounders: older maternal age (defined as > 35 years), marital status (being not married), less than college educated status, non-White race, Hispanic ethnicity, smoking prior to and during the pregnancy, chronic hypertension and chronic diabetes, twin and triplet or higher order birth, non-privately insured status, and use of WIC food during pregnancy.

Of particular interest, non-ART infertility treatment was shown to remain an important independent predictor for a range of maternal and infant outcomes after controlling for the above confounders. This is indicated by the computed adjusted odds ratios (which indicate the relative measure of risk compared to the SC group, with narrow confidence intervals in all cases) for pre-eclampsia (1.6), eclampsia (2.31), gestational diabetes (1.62) and non-vertex presentation in the mother (1.68), and low birthweight (1.67), preterm birth (1.59), need for assisted ventilation for more than 6 hours after delivery (1.80), admission to a neonatal intensive care unit (NICU, 1.87), and infant not being alive (or requiring transfer to a different facility) at the time of BC report (1.56).

Our findings add value to the information on maternal and infant characteristics from previous research on non-ART use in the US. Compared to the spontaneously conceived group, mothers who underwent non-ART infertility treatments were more likely to be White, have higher education and private insurance. They had a higher prevalence of co-morbidities and were at a higher risk of developing complications of pregnancy and labor. Infants conceived with non-ART treatments were at higher risk of plurality, and after controlling for twin and higher order births and several other confounders, were still at higher risk of prematurity and low birthweight, and NICU admission/ assisted ventilation. They were also at higher risk of not living to, or requiring transfer before, the time of BC reporting.

While a primary prevention approach focused on preventing the development of infertility in the first place would be ideal, our study results suggest further that policy efforts should best center on secondary and tertiary prevention. Specifically, efforts targeting individuals seeking infertility treatments (including non-ARTs) should attempt to limit and reduce poor maternal and infant events and outcomes during and after pregnancy. In light of our findings, therefore, it is also important for further research to demonstrate the safety of these treatments for mothers and infants, because the public health implications of these treatments for the health of women and children, and onsequently for the well-being of families overall, are far-reaching in both the short and long-term. Further, women (and their partners) need to have access to counseling concerning non-ART treatments including accurate information materials that are up-to-date, culturally, and linguistically competent.

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