Sex-related growth differences are present but not enhanced in in vitro fertilization pregnancies

Kathleen E. O'Neill, M.D.,[a] Methodius Tuuli, M.D., M.P.H.,[b] Anthony O. Odibo, M.D., M.S.C.E.,[b] Randall R. Odem, M.D.,[c] and Amber Cooper, M.D., M.S.C.I.[c]

[a] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and [b] Division of Maternal Fetal Medicine and [c] Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Washington University in St. Louis, St. Louis, Missouri

Objective: To determine whether IVF modifies the effect of fetal sex on growth.
Design: Retrospective cohort study.
Setting: Tertiary care center and related facilities.
Patient(s): Singleton live births without fetal/maternal comorbidities from fertile women who conceived without the use of assisted reproductive technologies and infertile women who conceived with IVF.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome was birth weight (BW). Secondary outcomes were fetal crown-rump length (CRL) in the first trimester, biparietal diameter (BPD), and estimated fetal weight (EFW) in the second trimester.
Result(s): There were no differences in baseline characteristics between women carrying male fetuses and those carrying female fetuses in either mode of conception. In unadjusted analyses, the male-female differentials in fetal BPD and BW were more pronounced in the IVF cohort than in the unassisted cohort. In multivariable regression analysis, male BPD exceeded female BPD by 0.12 cm, male EFW exceeded female EFW by 12 g, and male BW exceeded female BW by 172 g. IVF did not have a significant effect on BPD but was associated with a 52 g increase in EFW in the midgestation. IVF was associated with an 81-g reduction in BW. IVF did not modify the magnitude of size differences between the sexes in the midgestation or at birth.
Conclusion(s): Comparable sex-dependent differential growth occurs in unassisted and IVF pregnancies. (Fertil Steril® 2014;101:407–12. ©2014 by American Society for Reproductive Medicine.)
Key Words: Fetal sex, IVF, birth weight, gestational age

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Over the last 30 years, the use of assisted reproductive technologies (ART) has become increasingly common; in 2009, IVF and related technologies played a role in 1.4% of births in the United States (1). Thus, it is extremely important that we fully understand any potential risks of the IVF process, which involves laboratory manipulation of sperm and eggs, culture of embryos, and uterine transfer. Many studies have suggested that infants born as a result of assisted reproduction have significantly lower birth weights (BWs) than those who are conceived without ART (2–7). However, the mechanism behind this effect is not well understood, and there is still a debate about whether the effect is related to IVF itself, the underlying infertility, or both (8).

In unassisted term births, male infants are approximately 150 g heavier than female infants (9–11). Although this is often attributed to the higher concentrations of circulating androgens synthesized by the testes, it has been suggested that there are sex-associated differences in growth rate before differentiation of the fetal gonads. As a result, there has been disagreement about the point in development at which this difference begins and can be detected, with some investigators arguing that the difference does

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Reprint requests: Kathleen E. O'Neill, M.D., University of Pennsylvania, 3701 Market Street, Suite 800, Philadelphia, PA 19104 (E-mail: kathleen.o'neill2@uphs.upenn.edu).

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not become apparent until the second trimester and others contending that these differences are apparent at much earlier stages of development (12–21).

The differential XX-XY development rates have been studied extensively in animal models. Increased cell numbers were observed in XY embryos compared with in XX embryos as early as 3.5 days postcoitus in mice (22), and bovine male embryos were found to have developed to more advanced stages than females during the first 8 days after insemination in vitro (23). Research in humans has shown that crown-rump length (CRL) and biparietal diameter (BPD) in male fetuses were on average larger than female ones at the first measurement between the weeks 8 and 12 (13).

Given that in vitro culture of animal embryos has been shown to correlate with aberrant fetal and perinatal development (24, 25) and that IVF has been suggested to affect fetal growth (8), a key question about the safety of IVF is whether or not it enhances the growth differential between male and female fetuses.

Several studies have addressed this question in vitro. For example, animal studies have suggested that in vitro culture conditions enhance sex-dependent growth rates during preimplantation embryonic development (16). The sex of the embryo may influence the embryo's response to environmental stress, such as exposure to transient elevated temperatures during the culture period (26). Additional micromanipulation, such as intracytoplasmic sperm injection (ICSI), has been postulated to further affect sex-related growth differences in human embryos. In one study, the mean log cell number of male blastocysts after ICSI was significantly greater than that of similarly treated female embryos, whereas no such difference was found among conventionally inseminated IVF-derived embryos (9). In an effort to ascertain whether the sex-dependent growth differential was seen without micromanipulation and culture stressors, day 3 and 4 mouse embryos were recovered from reproductive tracts. In this study, female embryos compacted earlier than males in vivo, however, in vitro conditions supported the development of male embryos to the blastocyst stage (27). These data suggest that the increased cell proliferation observed in male embryos is an artifact caused by the in vitro environment. Similarly, no sex effect on size was seen in pig embryos flushed at 12 days' gestation (28). No study has yet examined the sex-dependent growth differential throughout pregnancy in a cohort of infertile couples undergoing IVF in comparison with a cohort of unassisted conceptions in a fertile cohort.

The objective of this study was to determine whether the effect of fetal sex on fetal growth is modified by IVF. We hypothesized that the differential growth observed between males and females in a population conceived without the assistance of ART would be present and enhanced in pregnancies conceived through the use of IVF.

MATERIALS AND METHODS

The Institutional Review Board at Washington University in St. Louis approved this study. The Society for Assisted Reproductive Technologies database was used to identify women 18–45 years of age with singleton live births conceived as a result of IVF from our unit between January 1, 1999, and February 1, 2009. We included only those with complete pregnancy and birth data in the Washington University Prenatal Genetics Ultrasound Database. This database comprises all patients seen in our prenatal diagnosis center and is maintained by a dedicated nurse coordinator. Each patient is given a standardized form requesting pregnancy outcome to be returned after delivery, and medical records are reviewed for accuracy. Demographic and health information is obtained before the visit through intake forms, and the information is reviewed and confirmed with patients at the time of their ultrasound. When a follow-up form is not returned within 4 weeks of the expected date of delivery, the patient receives a phone call from the coordinator. In cases where the patient cannot be contacted, her referring physician is contacted for outcome information. For patients delivering in our health care system, outcome data were extracted from our perinatal computerized database. On average, the survey return rate is over 90%.

A singleton live birth was defined as a viable infant delivered at 23 completed weeks or later in gestation with a fetal weight more than 500 g. Precise gestational dating for conceptions from IVF was by the date of oocyte retrieval. The IVF pregnancies were all fresh embryo cycles. Frozen embryo, donor oocyte, and cycles using testicular sperm extraction were excluded. All IVF cycles were performed according to standard controlled ovarian hyperstimulation protocols with gonadotropins and GnRH agonist or antagonist pituitary suppression, ultrasound-guided transvaginal oocyte aspiration, and transcervical ET. The number and timing of the ETs were individualized on the basis of clinical indications but were done on either day 3 or day 5.

A cohort of women 18–45 years of age with unassisted singleton live births between January 1, 1999, and February 1, 2009, was identified from the aforementioned prenatal ultrasound database. This cohort has been described elsewhere (8).

Exclusion criteria for both the IVF and unassisted conceptions included pregnancies with selective reduction, fetal chromosomal or major congenital anomalies, maternal pregestational diabetes, preexisting hypertension, renal disease, sickle cell disease, other major medical conditions, and tobacco use. Patients with a first-trimester spontaneous reduction of a second gestational sac were included but were adjusted for in the multivariable analyses. Maternal age was recorded as age at the time of delivery. Race/ethnicity was self-reported information, with patients subdivided into white, black, and other for analyses.

The primary outcome was the difference in weight at birth between male and female fetuses stratified by mode of conception. The secondary outcomes were differences in in utero fetal size as measured by BPD, estimated fetal weight calculated by the modified Hadlock model (EFW) (29) in midgestation, and CRL in the first trimester.

Statistical analyses were performed with STATA 11.0 SE software. Baseline characteristics between women carrying male and female fetuses were compared separately in unassisted and IVF-conceived pregnancies.