Sexual size dimorphism is thought to contribute to the greater mortality and morbidity of men compared with women. However, the timing of onset of sexual size dimorphism remains uncertain. The authors determined whether human fetuses exhibit sexual size dimorphism in the first trimester of pregnancy. Using a prospective cohort study, conducted in 1999–2002 in the United States, they identified 27,655 women who conceived spontaneously and 1,008 whose conception was assisted by in vitro fertilization or intrauterine insemination and for whom a first-trimester measurement of fetal crown-rump length was available. First-trimester size was expressed as the difference between the observed and expected size of the fetus, expressed as equivalence to days of gestational age. The authors evaluated the association between fetal sex, first-trimester size, and birth weight. Eight to 12 weeks after conception, males were larger than females (mean difference: assisted conception = 0.4 days, 95% confidence interval (CI): 0.1, 0.7, p = 0.008; spontaneous conception = 0.3 days, 95% CI: 0.2, 0.4, p < 0.00001). The size discrepancy remained significant at birth (mean birth weight difference: assisted conception = 90 g, 95% CI: 22, 159, p = 0.009; spontaneous conception = 120 g, 95% CI: 107, 132, p < 0.00001). These data demonstrate that human fetuses exhibit sexual size dimorphism in the first trimester of pregnancy.
Sexual size dimorphism is a feature of humans and non-human primates and is thought to contribute to the greater mortality and morbidity of men compared with women (1, 2). Across populations and races, men are approximately 8 percent taller and their longevity 8 percent shorter than that of women (3). Across species, longevity of the larger of the sexes is shorter (4). Animal studies have also demonstrated that male bias in mortality disappears after adjustment for weight difference between sexes (5). The association between sexual size dimorphism and longevity is biologically plausible because larger body size requires more cell divisions, which results in shorter telomere length. In turn, shorter telomere length is inversely related to mortality in humans (6). Compatible with this hypothesis, men have shorter telomeres and longevity than do women (6, 7). The onset of sexual size dimorphism in the human is unknown. Previous studies have suggested that birth weight is determined, at least in part, in the first 12 weeks after conception (8). Here, we show that human fetuses exhibit sexual size dimorphism in the first trimester of pregnancy.

MATERIALS AND METHODS

We analyzed data for 27,655 women who conceived spontaneously (SPON) and 1,008 who conceived as a result of conception assisted by in vitro fertilization or intrauterine insemination (ASC) from a previously described, prospective cohort study conducted in 1999–2002 in the United States (9). The ASC and SPON pregnancies were assessed separately to determine the effect of uncertainty regarding menstrual dating. Women in this cohort were followed throughout pregnancy, and data on pregnancy outcome, including birth weight, were collected prospectively. All pregnancies ended in livebirth of a singleton infant without evidence of chromosomal or congenital abnormality. Other fetal or maternal complications were not excluded. We measured fetal crown-rump length 8–12 weeks after conception by using ultrasound. All measurements were performed by specially trained ultrasound technicians according to a standardized protocol (10), and gestational age estimates were centrally calculated by using Hadlock criteria (11).

The observed size of the embryo or fetus was related to the expected size on the basis of the date of conception (estimated as 14 days after the first day of the last menstrual period for SPON pregnancies and precisely known for ASC pregnancies). The difference between the actual and predicted crown-rump length was expressed as the difference in days of gestation (Δ GA), that is, the estimated postconception age according to crown-rump length minus the estimated number of days after conception. Positive Δ GA values indicate a larger than expected fetus and negative values a smaller than expected fetus. We confined analysis of SPON pregnancies to those with a Δ GA of between −7 and 7 days because differences outside this range more likely reflect error in menstrual dating. The associations between Δ GA, fetal sex, and birth weight were modeled by using multivariable linear regression with fractional polynomials to assess linearity. The large size and composition of the study population from low-risk pregnancies enrolled in 15 centers representing all major geographic areas of the United States assure its representativeness and generalizability of the findings.
RESULTS

There were 28,663 pregnancies; 3.5 percent were considered ASC, and 51.1 percent of the fetuses were male. Eight to 12 weeks after conception, male fetuses were larger than females (mean difference: ASC = 0.4 days, 95 percent confidence interval (CI): 0.1, 0.7, p = 0.008; SPON = 0.3 days, 95 percent CI: 0.2, 0.4, p < 0.0001). The size discrepancy remained significant at birth (mean birth weight difference: ASC = 90 g, 95 percent CI: 22, 159, p = 0.009; SPON = 120 g, 95 percent CI: 107, 132, p < 0.0001) (figures 1 and 2).

The association between Δ GA and fetal sex was not materially affected by adjustment for maternal height, weight, parity, race, gestational age at delivery, and smoking status (adjusted coefficient: ASC = 0.4 days, 95 percent CI: 0.1, 0.7, p = 0.015; SPON = 0.3 days, 95 percent CI: 0.3, 0.4, p < 0.0001).

DISCUSSION

Previous studies have suggested that placental function in the first trimester of pregnancy is an important determinant of fetal growth, preterm birth, and risk of stillbirth (8, 12). Consistent with this finding, periconceptual manipulation of maternal diet alters the outcome of ovine pregnancy (13). Our data demonstrate that sexual size dimorphism is evident in the human fetus in the first trimester of pregnancy. We conclude that sex-dependent effects on size-related differences in morbidity and mortality in adult life (1, 2, 14) may be determined in the first weeks after conception.

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