Are semen parameters related to birth weight?

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Several experimental models suggest a link between maternal nutrition during gestation and reproductive function in offspring, but the impact of birth weight on male fertility in adulthood in humans is poorly documented. To study whether birth weight is associated with unexplained male subfertility later in life, we evaluated the relationship between birth weight and sperm parameters in adulthood in white subfertile men, partners of couples with primary idiopathic subfertility, and fertile men recruited within the ALIFERT (Diet and Its Relationship with Couple Infertility) study. Total sperm count, progressive motility, and sperm DNA fragmentation were analyzed in sperm, and metabolic assays were performed on blood. Birth weight was associated with sperm DNA fragmentation and inversely correlated with total sperm count, underlining the importance of the in utero environment for male reproductive function.

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The intrauterine environment may affect later health outcomes of the offspring. This fetal programming of metabolic diseases is now a well established concept known as DOHAD (Developmental Origins of Health and Disease). Little is known about prenatal development and subsequent gametogenesis and fertility in adulthood. Also, data in animal models suggest a link between maternal nutrition during gestation and reproductive function in offspring (1, 2).

In humans, it is difficult to retrospectively assess in utero nutrition, so birth weight (BW) is commonly used as a proxy for nutritional conditions during fetal life. François et al. previously reported that men born small for their gestational age (SGA) are more likely to present subfertility (3). More recently, Vanbillemont et al. demonstrated that BW is positively correlated with plasma testosterone concentrations (4). Olsen et al. and Ramlau-Hansen et al., however, did not confirm an association between BW and reproductive function (5, 6). Studies in women demonstrated that a low BW increases the risk of early reproductive senescence (7, 8) and that low (<2,500 g) and high (>4,500 g) BWs are associated with an increase in the time to pregnancy (9). In adolescent girls born SGA, anovulation is more common (10). These data indicate that either a low or a high BW may induce altered development of reproductive functions associated with subfertility in adulthood.

The present study aimed to investigate the relationship between BW and semen parameters in idiopathic subfertile men.

MATERIAL AND METHODS

Data from 92 white subfertile men (age range 23–45 years) and 91 white fertile men (age range 28–45 years) recruited within the ALIFERT (Diet and Its Relationship with Couple Infertility) study (Biomedical Research P071224) were recorded. Subfertile men were partners of couples with primary idiopathic subfertility. Fertile

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men were partners of couples with at least one child (<2 year old) spontaneously conceived, with a time to pregnancy <12 months. Inclusion criteria for the ALIFERT study excluded patients with current or previous metabolic (dyslipidemia, high blood pressure, hyperglycemia, diabetes, etc.) or digestive disease.

Subfertile couples were defined by an inability to conceive after 12 months of unprotected sex. It would be the first pregnancy of the couple. Men were compatible with a natural pregnancy sperm characteristics and were excluded if they presented: 1) severe oligozoospermia (<5 million/mL) or azoospermia (no sperm in the ejaculate); 2) moderate oligozoospermia (5–20 million sperm per mL) that was nonidiopathic, that is, that could be explained with certainty by one or more of the following factors: toxic (chemotherapy, radiotherapy, drugs known effects on spermatogenesis), infectious (mumps virus, chlamydia, mycoplasma), anatomic (vasectomy, congenital anomalies [absence of vas deferens], prolonged post-traumatic ischemia), endocrine (hypogonadotropic hypogonadism), or cytogenetic (Klinefelter syndrome, translocations, chromosome inversions); or 3) abnormality of the male genital tract: varicocele, cryptorchidism, undescended testicles, or testicular volume <12 mL. Women did not present anovulation, ovarian failure, or uterotubal pathology.

Anthropometric Assessment

BW and gestational length were collected from the childhood health records. All subjects were born at term (37–41 weeks of amenorrhea).

Height was measured to the nearest 5 mm, without shoes, on a metric scale by the same trained investigator. Waist circumference was measured at the narrowest point between the lower border of the ribs and the iliac crest. Weight and body composition were evaluated with the use of the Tanita BC-420 MA analyzer. The bioelectrical impedance measurement combines a digital scale with stainless steel pressure-contact footpad electrodes for standing impedance and body weight measurements (11). Details of the validation and performance characteristics of this bioimpedance analysis model have been reported previously (12).

Lifestyle Factors

During the inclusion of the couple, data on sociodemographic characteristics and age were collected. Also, all participants filled out a Pittsburgh Sleep Quality Index questionnaire to estimate quality of sleep, a tobacco questionnaire to evaluate tobacco consumption, and an International Physical Activity Questionnaire to estimate physical activity. Only age and tobacco factors affected results and were taken into account for the normalization of results.

Semen Analysis

Only subfertile men produced semen samples by masturbation into a specimen cup at the laboratory. Lubricants were not used for masturbation. The men were asked to abstain from ejaculation for 3–5 days before the clinic visit and to report the time of their previous ejaculation. Men who failed to follow these instructions were excluded. Samples were processed within 30 minutes of collection.

After semen liquefaction, semen analysis was performed according to World Health Organization guidelines (13) for assessing semen volume and sperm concentration. Total sperm count was calculated as concentration × volume. Motility was assessed, classifying the spermatozoa as progressive motile (A + B), total motile (A + B + C), or immotile (D).

Determination of Sperm DNA Integrity

To evaluate sperm nuclear DNA integrity, the terminal deoxynucleotide transferase–mediated dUTP nick-end labeling technique (13, 14) was performed on semen samples with the use of the In Situ Cell Death Detection Kit (Roche Applied Science). Briefly, after trypsinization, spermatozoa were fixed in Carnoy solution (2:1 methanol/acetic acid) and stored at −20°C. Sperm pellets were permeabilized for 20 minutes with 0.1% Triton X-100 in sodium citrate solution and washed with phosphate-buffered saline solution (PBS), and then cells were incubated with dUTP fluorescein isothiocyanate (FITC)–labelled and terminal deoxyribonucleotide tranferase (TdT; TUNEL solution).

The positive control sample was treated with 100 μL DNase (0.5 mmol/L) for 1 hour at 37°C before incubation with the TUNEL solution, and the TdT enzyme was omitted for the negative control. Cells were then washed twice in PBS and spread out over slides. Slides were dried at room temperature in the dark, and 6-diamino-2-phenylindole (DAPI) solution was added over the spermatozoa. Slides were examined with the use of fluorescence microscopy. At least 500 spermatozoa were counted, and total sperm DNA fragmentation rate was calculated as the number of FITC-positive cells from the total number of sperm nuclei (labeled with DAPI). Two investigators blinded to the exposure and other covariates performed the analyses.

Blood Collection

Blood samples were used to measure the fasting lipid profile (triglycerides, total cholesterol, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol).

Statistical Analysis

To determine whether there is a relationship between BW and sperm characteristics or anthropometric or metabolic profile, a Pearson correlation was used for correlation analysis. A value of $\leq .05$ was considered to be statistically significant. A *t* test was used for comparing fertile versus subfertile. The normality of BW data was verified with the use of the Shapiro test. It was normal ($P = .34$).

Institutional Review Board Approval

The study was conducted according to the protocol, to the law of December 20, 1988, as amended by Act 2004-806 of August 9, 2004, to the ethical principles established by the 18th World Medical Assembly, and to French Good Clinical Practice. Before starting the research, an authorization file (as defined in Article L 1123-12) was approved by Agence Française de