Fetal exposure to maternal stress and male reproductive function in a cohort of young adults

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Objective: To study associations between maternal stress during pregnancy and reproductive function in young men.
Design: A cohort study nested in a population-based birth cohort.
Setting: Not applicable.
Patients: Young men (n = 1,052; response rate, 19%) participated in the Fetal Programming of Semen Quality cohort from 2017 to 2019. They were recruited from pregnancies in the Danish National Birth Cohort (1996–2001). The men completed an online questionnaire, clinical examination, and collection of blood and semen samples.
Exposures: Information on maternal life and emotional stresses was available from a telephone interview covering the interval from the beginning of pregnancy to approximately gestational week 30.
Main Outcome Measure(s): We applied negative binomial, linear, and logistic regression to examine associations between life and emotional stress scores (range, 0–18) and reproductive function. The primary outcomes were measures of semen quality, and the secondary outcomes included reproductive hormone levels and testicular volume.
Result(s): Overall, we observed no negative associations between maternal life or emotional stress and male reproductive function. Maternal emotional stress was associated with higher total sperm count (16% difference; 95% confidence interval [CI], 1–33), serum estradiol (11% difference; 95% CI, 2–21), and calculated free testosterone ($\beta = 17.8$; 95% CI, 1.26–34.3). The results were robust to inverse probability weighting introduced to account for selection.
Conclusion(s): Although our findings may appear reassuring, further efforts to validate the measures of stress during pregnancy and improve our understanding of the full spectrum of fetal stress exposures and consequences for health later in life are needed. (Fertil Steril® 2022;117:1255–65. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Prenatal stress, maternal stress, semen quality, reproductive hormones, male fertility

While the transition to motherhood can be a time of expectation and joy for many, the radical physical, psychological, and social changes imposed by pregnancy often bring frustrations and worries as well (1). In addition, stressful life events unrelated to the actual pregnancy may contribute to

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generation of excess maternal stress. The burden of maternal stress is shared by the developing fetus with growing evidence of developmental and otherwise adverse effects for a range of child-health outcomes (2–6).

As several essential aspects of male reproductive function are determined prenatally through the process of fetal programming, male offspring may be sensitive to maternal stress depending on the nature, timing, and intensity of stressors during pregnancy (7–10). Evidence of adverse reproductive effects of maternal stress in animals involve reductions in both semen quality and hormone levels due to changes in the morphology of testicular tissues and hypothalamic-pituitary-gonadal axis functions (11, 12). Studies on the potential association between prenatal exposure to maternal stress and male reproductive function in humans are still few (8, 10, 13). In population-based studies, sons with prenatal exposure to maternal bereavement have demonstrated a higher risk of congenital malformations and a reduced probability of fathering children (8, 13, 14). In addition, a study assessing reproductive function in young adult sons of mothers from a previously established pregnancy cohort (Raine) reported negative associations between exposure to stressful life events in early gestation and measures of both semen quality and reproductive hormones (10).

Although bereavement and other stressful life events may be applicable as the objective measures of relatively severe distress, our responses to facing challenges and adversity are highly individual (15). Our appraisal of hardship is the result of a complex cognitive process involving the actual input, previous experiences, coping strategies, and support from our surroundings (15). Further, the neuroendocrine response elicited and its potential effects on a fetus may depend on the specific type of stressor or stress involved (6, 16). Therefore, this study aimed to assess associations between 2 separate self-reported measures of stress, burdening from life and emotional stresses, during pregnancy and reproductive function in young adult male offspring. On the basis of the findings from previous studies in humans and animals, we hypothesized that maternal stress would have a negative impact on semen quality, reproductive hormone levels, and testicular volume.

MATERIALS AND METHODS

The Fetal Programming of Semen Quality Cohort

The establishment of the Fetal Programming of Semen Quality (FEPOS) cohort has been described in detail previously elsewhere (17). In brief, the Danish National Birth Cohort (DNBC) contains nationwide information on 101,042 pregnancies in Denmark from 1996 to 2002 with an estimated participation rate at enrollment of approximately 60% of the invited women (18–20). These women represented the primary sampling generation (F0) in our study and contributed information through both gestational blood sampling and computer-assisted telephone interviews in gestational weeks 16 and 30 (17). Adult sons (F1) were sampled randomly among F0-indexed women registered in the DNBC (17). The F1 men were required to be at least 18 years and 9 months of age and live within reasonable distance of 1 of the 2 study centers in Copenhagen and Aarhus (17). Young men with a history of cancer treatment, sterilization, or orchiectomy were considered ineligible (17). Recruitment spanned the years 2017–2019 with the inclusion of 1,058 men (5,697 invited men; response rate, 19%) through a secure digital mailbox system (e-Boks). A financial compensation of 500 DKK (approximately 67 Euro) was provided for all participants. Each man was provided thorough oral and written information before consenting for participation.

Participating men completed an extensive online questionnaire and provided semen and blood samples as part of a standardized clinical examination. All questionnaire and clinical data were collected and managed using SurveyXact (Ramboll, Copenhagen, Denmark). We extracted further information on all men through linkage of their unique Danish 10-digit personal identification number (Central Personal Register number) and the Danish Medical Birth Register (Medical Birth Registry) (21). This register has kept detailed records on all births in Denmark since 1973 including information on maternal age and parity at delivery (22).

With the specific aim of our current study in mind, we excluded 6 participating men from analyses for not having both testicles in the scrotum at the time of participation. Our final study population, therefore, consisted of 1,052 men.

Maternal Stress

The measures of maternal life and emotional stresses during pregnancy were based on information from the second telephone interview with the mothers. Here, life and emotional stresses were assessed using 9 items for each covering the entire interval from the beginning of pregnancy to week 30 of gestation (Table 1) (23). Life stress items were based on the Life Events Questionnaire focusing on burdening in several important domains of life (24). Emotional stress was measured through a combination of items from the Symptom Checklist 92 and the General Health Questionnaire 60 addressing feelings of anxiety, depression, and stress (Table 1) (3, 25, 26). All items were initially translated and adapted to the conditions of the telephone interview, limiting the number and length of both items and response categories (no, 0; a little, 1; and a lot, 2) (4). Internal consistency for related emotional stress items was assessed using Cronbach's alpha coefficients. When items related to anxiety, depression, and stress were assessed separately, consistency was relatively poor (coefficients of 0.56, 0.51, and 0.46, respectively). However, the coefficient for all emotional stress items combined was acceptable (0.73). Thus, we decided not to assess anxiety, depression, and stress items separately and applied only a combined score for all items.

Two sum scores for all items were calculated for life and emotional stresses separately (range, 0–18) (6). Categories were defined by cutoffs as close to the distribution tertiles as possible (low, 0 [n = 257]; medium, 1–2 [n = 456]; and high, ≥3 [n = 339], for life stress scores and low, 0–1 [n = 398]; medium, 2–3 [n = 314]; and high, ≥4 [n = 340] for emotional stress scores).

TABLE 1

Adapted inventory on maternal stress during pregnancy and distribution of answers among the mothers of the 1,052 young men in the Fetal Programming of Semen Quality cohort.

Life stress	Origin	No n (%)	A little n (%)	A lot n (%)
Question: Have you been burdened by…				
…financial troubles	LEQ	915 (87)	118 (11)	19 (2)
…your housing situation	LEQ	902 (86)	114 (11)	36 (3)
…your work situation	LEQ	706 (67)	263 (25)	83 (8)
…the relations to your partner	LEQ	944 (90)	90 (9)	18 (2)
…relations to family and friends	LEQ	966 (92)	74 (7)	12 (1)
…the pregnancy itself	LEQ	545 (52)	391 (37)	116 (11)
…disease yourself	LEQ	849 (81)	146 (14)	57 (5)
…disease in family or close friends	LEQ	916 (87)	94 (9)	42 (4)
…other things	LEQ	979 (93)	43 (4)	30 (3)
Burdened by at least 1 of the above		257 (24)	708 (67)	287 (27)

Emotional stress	Origin	Aspect	No n (%)	A little n (%)	A lot n (%)
Question: Have you…					
…felt frightened or anxious for no reason	SCL-92	Anxiety	791 (75)	233 (22)	28 (3)
…felt nervous or at unease	SCL-92	Anxiety	704 (67)	329 (31)	19 (2)
…felt tense or agitated	SCL-92	Anxiety	671 (64)	353 (34)	28 (3)
…felt that the future looked hopeless	SCL-92	Depression	947 (90)	94 (9)	11 (1)
…felt sad and blue	SCL-92	Depression	648 (62)	376 (36)	28 (3)
…felt that everything was a big effort	SCL-92	Depression	840 (80)	183 (17)	29 (3)
…felt under a constant pressure	GHQ-60	Stress	910 (87)	123 (12)	19 (2)
…been more touchy or quick-tempered than usually	GHQ-60	Stress	443 (42)	521 (50)	88 (8)
…felt that the demands on you were too big	GHQ-60	Stress	840 (80)	188 (18)	24 (2)
Troubled by at least 1 of the above			182 (17)	860 (82)	164 (15)

Note: GHQ-60 = General Health Questionnaire 60; LEQ = Life Event Questionnaire; SCL-92 = Symptom Checklist 92.

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Male Reproductive Function

Semen quality. Semen quality measures served as our primary outcomes. Semen samples were collected by masturbation with a recommended 2–4 days of abstinence from last ejaculation. Participants collected the sample either at 1 of 2 study centers or at home. For home collection, participants were sent a sterile polypropylene sample kit with careful instructions for transportation preferably at body temperature level. Semen analyses were initiated on arrival of the sample at the laboratory (83.6% of samples within 1 hour and 99.6% of samples within 2 hours of ejaculation). Specific abstinence time and potential spillage were recorded, and semen volume was measured by weight (1 g = 1 mL) (17). Subsequent processing and assessment of sperm concentration, total sperm count, motility, and morphology were performed in accordance with the specific recommendations from the World Health Organization 2010 by a trained laboratory technician (1 at each study center) (17, 27). In addition to running systematic internal comparisons, an external quality control program was set up with the Reproductive Medicine Centre in Malmö, Sweden, to ensure the reliability of selected measures. Comparing the results of FEPOS technicians to those of a reference laboratory, acceptable coefficients of variation (CVs) were observed for both sperm concentration and motility (FEPOS and reference CVs of 18.4% and 17.6%, respectively, for sperm concentration and 12.7% and 38.6%, respectively, for sperm motility in January 2018 based on 5 samples) (17).

Reproductive hormones. Reproductive hormone levels were considered the secondary outcomes. Blood samples were drawn from an antecubital vein using a VACUETTE Safety Blood Collection Set with Holder (Greiner Bio-One GmbH, Kremsmünster, Austria). The time of sampling was noted for each participant. Samples were centrifuged, and serum was stored in CryoPure Tubes (Sarstedt, Nümbrecht, Germany) at −80°C until analysis at the Department of Clinical Biochemistry at Aarhus University Hospital, Aarhus, Denmark.

The testosterone and estradiol levels were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (AB Sciex 6500 QTRAP, Framingham, MA). The limits of detection were 0.12 nmol/L for testosterone and 15 pmol/L for estradiol. The CV for testosterone was 7% at 14.1 nmol/L, whereas that for estradiol was 7.5% at 106 pmol/L. We determined the calculated free testosterone (CFT) using the formula by Vermeulen et al. (28) assuming a constant albumin concentration of 43 g/L.

The follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone-binding globulin levels were

measured using immunoassays (Cobas 8000 e602; Roche Diagnostics, Mannheim, Germany) with CVs of 2.5%–2.8%, 0.7%–1.2%, and 1.1%–1.7%, respectively. The limits of detection were 0.1 IU/L for FSH and LH and 0.350 nmol/L for sex hormone-binding globulin.

Testicular measurement. Testicular volume was included as a secondary outcome and assessed through self-measurement during clinical examinations using a Prader orchidometer. This method has been validated previously among Danish men (29).

Statistical Analyses

Initially, we examined the distribution of scores for life and emotional stress items by the number and percentage of participants. The distributions of the sum scores for life and emotional stresses were assessed graphically using histograms and through calculation of percentiles. Correlations between the life and emotional stress sum scores were assessed using Spearman's ρ.

Next, we stratified multiple covariates and outcome variables according to the sum scores. Our primary semen quality outcomes followed nonnormal distributions, and several outcome variables also contained values of 0. Negative binomial regression yielded the best fit for these analyses with the estimation of percentage differences $((\exp(\beta) - 1) \times 100)$ in semen characteristics between the low and medium or high maternal stress exposure groups. We restricted the analyses of total sperm count and semen volume to samples from men reporting no spillage (n = 866). In the analyses of motility and morphology, men with azoospermia were excluded (n = 17). Morphology data were unavailable for 6 men, and these were excluded from analyses of morphology.

Reproductive hormone levels were also analyzed using negative binomial regression apart from CFT, which was examined with multiple linear regression. Testicular size was calculated as the average volume for both testicles. The 12 volumetric ellipsoids in the Prader orchidometer constitute a measuring range from 1 to 25 mL with uneven intervals. We, therefore, analyzed the average testicular volume both as a count variable using negative binomial regression and as a dichotomized outcome (<15 and ≥ 15 mL) using logistic regression.

We constructed directed acyclic graphs on the basis of the existing literature for a priori selection of potential confounder variables (Supplemental Fig. 1, available online) (30). Consequently, all regression estimates were adjusted for maternal age (continuous, years), parity at delivery (number of births), and self-reported family occupational status during pregnancy. The latter was defined as the highest grade of occupation among the parents (high-grade professional, low-grade professional, skilled worker/unskilled worker, and student/economically inactive) (31). To examine direct associations for maternal stress not mediated by secondary changes in health behavior, we included adjustment for maternal smoking during pregnancy (self-reported nonsmoking; light smoking, ≤ 10 cigarettes/day; and heavy smoking, >10 cigarettes/day) in our main model. This approach was based on the assumptions of no unmeasured exposure-outcome, exposure-mediator, or mediator-outcome confounding and no known mediator-outcome confounders affected by the exposure. Further, we assumed no exposure-mediator interaction (32). However, we also performed analyses without adjustment for maternal smoking in a separate model.

In addition, regression models were adjusted for precision variables potentially associated with the specific outcomes. Thus, semen quality outcomes were adjusted for abstinence time (continuous, days), sampling site (home/clinic), spillage (yes/no) (for sperm concentration, motility, and morphology), and time from ejaculation to analysis (continuous, min) (for motility). Reproductive hormones were adjusted for time of blood sampling (morning, before 12 noon; midday, 12–18 PM; and evening, after 18 PM) and body mass index (<18.5, 18.5–24.9, 25–29.9, and >30 kg/m^2). Testicular volume was adjusted for abstinence time (continuous, days). Self-reported questionnaire information on current or previous urogenital disorders (mumps orchitis, hydrocele, varicocele, torsion of testis, cryptorchidism, hypospadias, and phimosis) potentially related to male reproductive function was included in all adjustments.

We applied inverse probability weighting (IPW) in a separate model to examine selection into the FEPOS cohort among all invited young men. Weighting was assigned according to several baseline characteristics (maternal prepregnancy body mass index, age, parity at delivery, smoking and alcohol consumption, time to pregnancy, and family occupational status and region of residence during pregnancy) chosen a priori through directed acyclic graphs (Supplemental Fig. 2, available online). Men with incomplete information on these characteristics were excluded from this model (n = 54). With the IPW approach, bias from selection was accounted for in relation to information available from both participants and nonparticipants.

In an additional sensitivity analysis, we examined associations for a greater exposure contrast with a combined sum score for both life and emotional stresses (range, 0–36) categorized according to the distribution tertiles (low, 0–2; medium, 3–5; and high, >5). Finally, we examined contributions from issues related to the pregnancy itself or maternal somatic disease through the assessment of associations for life stress items individually.

All estimates were based on information from at least 5 individuals (e.g., calculated pseudo medians and percentiles) according to national data protection regulations. Statistical analyses were performed using Stata V. 15 (StataCorp, College Station, TX).

Ethics

The FEPOS study was conducted in accordance with the principles of the Declaration of Helsinki. All participants gave written informed consent before their inclusion in the study. Approvals were obtained from the Regional Scientific Ethical Committee for Copenhagen and Frederiksberg (H-16015857) and the Steering Committee of the DNBC. Further, the project was approved by the Knowledge Centre on Data Protection Compliance under the records of processing regarding health

TABLE 2

Characteristics of the Fetal Programming of Semen Quality cohort stratified by maternal stress score levels during pregnancy.

	Life stress score			Emotional stress score		
	Low (0)	Medium (1–2)	High (≥3)	Low (0–1)	Medium (2–3)	High (≥4)
Mothers						
Age at index birth, mean (SD)	31.0 (3.9)	30.9 (4.3)	31.1 (4.2)	31.4 (4.1)	31.0 (4.0)	31.5 (4.4)
Parity (first birth), n (%)	135 (53)	211 (46)	119 (35)	171 (43)	144 (46)	150 (44)
Body mass index, median ($P_{5\%}$, $P_{95\%}$) [a]	22.5 (19.0, 30.0)	22.0 (18.3, 29.3)	22.0 (18.1, 29.9)	22.3 (18.7, 29.5)	22.0 (18.2, 29.5)	22.0 (18.2, 30.3)
Smoker, n (%)	44 (17)	103 (23)	95 (28)	63 (16)	74 (24)	105 (31)
Alcohol drinking weekly ≥1 unit, n (%) [b]	132 (51)	214 (47)	152 (45)	196 (49)	154 (49)	148 (44)
High-grade family occupational status, n (%) [c]	81 (32)	156 (34)	118 (35)	137 (35)	105 (33)	113 (33)
Young men						
Eligible men, n	257	456	339	398	314	340
Body mass index, median ($P_{5\%}$, $P_{95\%}$)	21.9 (18.4, 28.0)	22.2 (17.9, 28.7)	21.9 (17.7, 27.9)	21.9 (17.9, 28.1)	22.1 (18.0, 28.7)	22.1 (18.0, 27.8)
Smoker weekly, n (%)	101 (39)	168 (37)	143 (42)	147 (37)	126 (40)	139 (41)
Alcohol drinker weekly, n (%)	142 (55)	224 (49)	196 (58)	210 (53)	176 (56)	176 (52)
Urogenital disorder, n (%) [d]	48 (19)	73 (16)	65 (19)	66 (17)	53 (17)	67 (20)
Clinical examinations						
Abstinence time, n (%)						
<2 days	87 (34)	156 (34)	119 (35)	123 (31)	116 (37)	123 (36)
2–4 days	159 (63)	272 (60)	204 (60)	249 (63)	186 (59)	200 (59)
≥5 days	8 (3)	26 (6)	16 (5)	22 (6)	11 (4)	17 (5)
Spillage (yes), n (%)	46 (18)	80 (18)	54 (16)	61 (16)	52 (17)	67 (20)
≤1 h to sample analysis, n (%) [e]	206 (81)	375 (83)	287 (85)	321 (82)	260 (83)	287 (84)
Sampling site (clinic), n (%)	212 (83)	394 (87)	298 (88)	338 (86)	268 (86)	298 (88)
Place of analysis (Copenhagen), n (%)	199 (78)	368 (81)	258 (76)	316 (80)	248 (79)	261 (77)
Time of blood sampling (morning), n (%)	94 (37)	166 (37)	115 (35)	151 (38)	112 (36)	112 (33)

Note: Medians and other percentiles are displayed as pseudo percentiles based on 5 adjacent values. P = percentile; SD = standard deviations.
[a] Prepregnancy body mass index (kg/m^2).
[b] In the first trimester.
[c] Based on the highest grade of either maternal or paternal occupational status during pregnancy.
[d] Current or previous urogenital disorder potentially related to reproductive function.
[e] Time from ejaculation to sample analysis.

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science research projects within the Capital Region of Denmark (P-2019-503) in accordance with regulations from the Danish Data Protection Agency.

RESULTS

Most of the 1,052 young men in this study were exposed to maternal life stress and/or emotional stress (76% and 83%) during pregnancy. Exposure to emotional stress was more frequent regarding mild symptoms, whereas burdening from life stress was more often severe (Table 1). Life stress was predominantly related to the actual pregnancy (48%), maternal disease (19%), or occupational conditions (33%). Emotional stress counted especially being more touchy (58%), sad (38%), or tense (36%) covering aspects of both stress, depression and anxiety. A full overview of scores for the individual stress items is shown in Table 1.

The distributions for both stress scores were right-skewed with a median score of 2 for both life stress (5th percentile, 0; 95th percentile, 6) and emotional stress (5th percentile 0; 95th percentile, 8). The sum scores for life and emotional stresses were moderately correlated (Spearman's ρ, 0.45). In Table 2, the characteristics of the FEPOS cohort are presented according to maternal life and emotional stress score categories.

TABLE 3

Negative binomial regression analyses of semen quality outcomes and testicular volume in relation to maternal stress score levels among the men in the Fetal Programming of Semen Quality cohort.

			Life stress score		
			Low (0)	Medium (1–2)	High (≥3)
Outcome	**Model**	**N**	**Ref**	**% diff (95% CI)**	**% diff (95% CI)**
Sperm concentration, 10^6/mL	Crude	1,046	-	−2 (−14, 12)	−4 (−17, 11)
	Adjusted	1,016		−8 (−20, 5)	−8 (−20, 7)
Semen volume, mL	Crude	861		0 (−8, 8)	0 (−8, 9)
	Adjusted	835		0 (−8, 8)	0 (−8, 8)
Total sperm count, 10^6	Crude	862		2 (−13, 20)	2 (−14, 21)
	Adjusted	835		−3 (−16, 12)	6 (−9, 23)
Motility, % nonprogressive/ immotile	Crude	1,029		0 (−6, 6)	−1 (−7, 6)
	Adjusted	994		0 (−6, 6)	−2 (−9, 5)
Morphology, % normal	Crude	1,023		−2 (−11, 9)	1 (−9, 13)
	Adjusted	994		−4 (−14, 7)	0 (−11, 12)
Average testicular volume, mL	Crude	-		4 (−1, 10)	4 (−2, 10)
	Adjusted	1,023		4 (−1, 10)	3 (−2, 10)
			Emotional stress score		
			Low (0–1)	**Medium (2–3)**	**High (≥4)**
Outcome	**Model**	**N**	**Ref**	**% diff (95% CI)**	**% diff (95% CI)**
Sperm concentration, 10^6/mL	Crude	1,046	-	−5 (−17, 8)	−3 (−14, 11)
	Adjusted	1,016		−1 (−13, 12)	2 (−10, 16)
Semen volume, mL	Crude	861		−2 (−9, 6)	1 (−7, 9)
	Adjusted	835		0 (−7, 8)	0 (−7, 8)
Total sperm count, 10^6	Crude	862		2 (−13, 18)	9 (−7, 26)
	Adjusted	835		7 (−6, 23)	16 (1, 33)
Motility, % nonprogressive/ immotile	Crude	1,029		−3 (−9, 3)	0 (−6, 6)
	Adjusted	994		−3 (−9, 3)	−1 (−7, 5)
Morphology, % normal	Crude	1,023		6 (−4, 17)	5 (−5, 17)
	Adjusted	994		6 (−4, 18)	5 (−6, 16)
Average testicular volume, mL	Crude	-		3 (−2, 8)	2 (−2, 8)
	Adjusted	1,023		3 (−3, 8)	3 (−2, 8)

Note: All semen quality outcomes and testicular volume were adjusted for parity, maternal age and smoking, family occupational status, abstinence time, and urogenital disorders. Information on spillage was included in adjustments for sperm concentration, motility, and morphology, whereas men reporting spillage were excluded from the analyses of semen volume and total sperm count (n = 180). Men with azoospermia were excluded from analyses of motility and morphology (n = 17). Similarly, men with unavailable morphology data were excluded from morphology analyses (n = 6) and men without testicular measures were excluded from analyses of testicular volume (n < 5). CI = confidence interval; diff = difference; Ref = reference.

Ugelvig Petersen. Maternal stress and male reproduction. Fertil Steril 2022.

The percentage of first-time mothers was higher among those with lower life stress scores. In addition, the percentage of smokers among both the young men and their mothers was higher among those in the high life and emotional stress score categories.

Outcome percentiles for the low-, medium-, and high-exposure categories are shown in Supplemental Table 1 (available online). The calculated pseudo medians for sperm concentration, total sperm count, and estradiol and CFT concentrations were slightly higher among men in the high-exposure categories. In regression analyses, there were no clear indications of negative associations between life and emotional stress exposures and measures of male reproductive function (Tables 3 and 4). Exposure to maternal emotional stress was associated with a higher total sperm count (16% difference; 95% confidence interval [CI], 1–33) and higher serum concentrations of estradiol (11% difference; 95% CI, 2–21) and CFT ($\beta = 17.8$; 95% CI, 1.26–34.3) (Tables 3 and 4). The findings from dichotomized analyses of testicular volume using logistic regression (Supplemental Table 2, available online) were in line with those from the negative binomial regression model. Analyses without adjustment for maternal smoking in a separate model added no substantial changes to our results (Supplemental Tables 3 and 4, available online). In our IPW analyses, the baseline characteristics with the strongest relation to participation were the region of residence, maternal alcohol consumption, and smoking (*P* values of .00, .01, and .03 in the life stress model and *P* values of .00, .01, and .05 in the emotional stress model, respectively). Our results were robust to the introduction of IPW in analyses (Supplemental Tables 5 and 6, available online). Considering either the combined sum scores or the individual life stress items, we found no strong associations with any reproductive outcomes (Supplemental Tables 7, 8, and 9, available online).

DISCUSSION

In this study of fetal exposure to maternal life and emotional stresses and adult male reproductive function, we found no indications of any negative associations.

TABLE 4

Regression analyses of reproductive hormone levels in relation to maternal stress score levels among the men in the Fetal Programming of Semen Quality cohort.

			Life stress score		
			Low (0)	Medium (1–2)	High (≥3)
Negative binomial regression	**Model**	**N**	**Ref**	**% diff (95% CI)**	**% diff (95% CI)**
Testosterone, nmol/L	Crude	1,040	-	−1 (−5, 4)	2 (−3, 7)
	Adjusted	1,015		−1 (−5, 4)	1 (−3, 6)
Estradiol, pmol/L	Crude	1,040		7 (−2, 17)	9 (0, 19)
	Adjusted	1,015		7 (−3, 16)	9 (−1, 19)
FSH, IU/L	Crude	1,039		7 (−4, 19)	2 (−7, 12)
	Adjusted	1,014		9 (−3, 21)	3 (−6, 13)
LH, IU/L	Crude	1,039		3 (−4, 10)	−1 (−8, 5)
	Adjusted	1,014		3 (−4, 10)	−1 (−7, 5)
SHBG, nmol/L	Crude	1,039		−1 (−7, 5)	1 (−5, 8)
	Adjusted	1,014		0 (−6, 5)	−1 (−7, 4)
Linear regression	**Model**	**N**	**Ref**	**β (95% CI)**	**β (95% CI)**
CFT, pmol/L	Crude	1,039		−1.6 (−18.8, 15.5)	2.6 (−15.6, 20.9)
	Adjusted	1,014		−4.1 (−21.8, 13.5)	3.0 (−15.0, 21.0)
			Emotional stress score		
			Low (0-1)	Medium (2–3)	High (≥4)
Negative binomial regression	**Model**	**N**	**Ref**	**% diff (95% CI)**	**% diff (95% CI)**
Testosterone, nmol/L	Crude	1,040	-	1 (−3, 6)	2 (−2, 7)
	Adjusted	1,015		2 (−2, 7)	4 (−1, 8)
Estradiol, pmol/L	Crude	1,040		6 (−3, 15)	11 (2, 20)
	Adjusted	1,015		6 (−3, 15)	11 (2, 21)
FSH, IU/L	Crude	1,039		−6 (−16, 5)	−7 (−16, 4)
	Adjusted	1,014		−5 (−15, 7)	−8 (−16, 2)
LH, IU/L	Crude	1,039		−3 (−9, 4)	−4 (−9, 3)
	Adjusted	1,014		−2 (−9, 5)	−3 (−9, 3)
SHBG, nmol/L	Crude	1,039		−1 (−7, 4)	−2 (−7, 4)
	Adjusted	1,014		0 (−6, 5)	1 (−5, 7)
Linear regression	**Model**	**N**	**Ref**	**β (95% CI)**	**β (95% CI)**
CFT, pmol/L	Crude	1,039		7.7 (−8.8, 24.3)	14.2 (−2.0, 30.4)
	Adjusted	1,014		9.6 (−6.6, 25.9)	17.8 (1.26, 34.3)

Note: All hormone outcomes were adjusted for time of blood sampling, body mass index and urogenital disorders of the man, family occupational status, maternal age, smoking, and parity. CFT = calculated free testosterone; CI = confidence interval; diff = difference; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone-binding globulin; Ref = reference.

Ugelvig Petersen. Maternal stress and male reproduction. Fertil Steril 2022.

Previous epidemiological studies differ regarding the timing, nature, and intensity of maternal exposures examined, limiting direct comparability of results to those of our cohort (8, 10, 13). Recently, Bräuner et al. (10) examined associations between fetal exposure to maternal stressful life events in both early and late gestation (weeks 18 and 34 of pregnancy) and male reproductive function in an offspring cohort of young men (n = 643, of whom 326 provided semen samples). Here, only early gestational stressful life events were negatively associated with the total sperm count, number of progressively motile sperm, and morning serum testosterone (10). The basic development of the male reproductive organs occurs from approximately 7–15 weeks of gestation in humans (7). Conditions during this critical window of male programming may define the final reproductive capacity of individuals later in life. The specific timing of fetal exposures during pregnancy is, therefore, of particular interest in studies of male reproductive function. In our study, the applied measures of maternal stress are based on information from the third trimester covering the entire span from the beginning of pregnancy to gestational week 30. As recent symptoms may be more reliably reflected in item responses than those presenting in early pregnancy, recalling stress over time may introduce misclassification of exposures. Further, a single assessment may not adequately capture fluctuations in conditions, and actual stress levels at various points throughout the pregnancy may be underestimated. While uncertainties regarding the specific timing of exposure may bias our results in either direction of a true association, the bias will most likely be toward the null. On the other hand, our chosen measures of stress represent rather persistent states with no likely distinct starting or ending points (9).

Psychosocial stress is a multidimensional concept covering a wide range of interactions with our environment and our personal resources available to process them (33, 34). In previous studies on male reproductive function, the measures of stress exposures in pregnancy have been equated primarily from stimuli (stressful life events, such as

bereavement) with little information on actual maternal appraisal of events (8, 10, 13). Feelings and thoughts about the uncontrollability, unpredictability, and manageability of life can, however, be captured by the measures of perceived stress. Correlations between the measures of perceived stress and stressful life events have in the past proven weak to moderate with considerable cultural variation in risk factors (33, 35). Stressful life events are more often closely related to demographic factors and tend to cluster in the lives of women of lower socioeconomic status (35). However, circumstances may be normalized through previous experiences or similarity in conditions among peers leaving little or no impact on overall well-being (35). Thus, the measures of perceived stress and stressful life events seem to assess different aspects of stress—with shared elements (35). In our study, the measures of especially life stress are quite similar to the previously applied inventories for stressful life events in the identification of specific stressors (10, 36). Our emotional stress items cover several issues of perceived stress with an additional focus on symptoms of depression and anxiety.

Our applied measures of life and emotional stresses combine information on several important domains from modified psychometric screening tools (24–26). We were, thus, able to cover the common aspects of burdening and negative feelings rated by severity with most women experiencing mild stress during pregnancy. Going through pregnancy is almost synonymous with being slightly touchy, tense, or sad, and intermittent emotional stress is considered quite normal during this time, as increasing hormone levels especially in the first trimester often manifest as mood swings (37). Adding scores across items for life and emotional stresses, the distribution among the expecting mothers of our cohort was skewed with mainly low scores and little variability. Our findings should be interpreted in the light of this limited exposure contrast, which may well be explained by selective enrollment of pregnancies in the DNBC with an underrepresentation of women with a lower socioeconomic and single status and, thus, potentially lower incidence of severely stressful life events (19). The DNBC interviews were very extensive covering multiple aspects of health and a number of diverse exposures during pregnancy. To limit the response burden on participating women, the full range of potential items and corresponding intensity scales were condensed in the DNBC interviews. While the internal consistency in stress scores for related domains remained overall acceptable in our study, the truncation of both items and response options may also have compromised the available contrasts in exposures to a certain extent. Further, the shortened versions of the psychometric tools applied have not been validated for use in a population of pregnant women, such as those interviewed in the DNBC.

Despite the use of psychometric tools, the self-reported measures of stress may not correlate well with actual changes in maternal stress biomarkers during pregnancy (38). A wide range of hormones, enzymes, neurotransmitters, and proinflammatory cytokines serve as endogenous signals of stress in a delicate network of compensatory regulation and nonlinear interactions (39). Some of these compounds cross the placental barrier and enter the fetal circulation (8). Thus, the integration of measures of selected biomarkers of especially chronic stress may improve future studies on fetal exposures (40). However, the actual interpretation of maternal or fetal stress biomarker levels will likely remain challenging. Approaches combining subjective and objective measures (e.g., observer-based assessment and register data) of stress may allow us to see past issues with unawareness and denial and provide more reliable and robust exposure assessments (41).

In addition to eliciting a complex physiological response, stress is associated with secondary changes in health behavior (e.g., smoking habits, sleeping patterns, dietary choices, alcohol consumption, exercise, and compliance with medical treatment) (39, 42). Limited resources often limit our ability to make good choices. The effects of stress may, therefore, be mediated by other risk factors for disease or dysfunction (43). In our study, we attempted to account for potential mediation of effects through maternal smoking. For other aspects of maternal health behavior, associations between fetal exposure and reproductive function later in life are not well established (44). Changes in heath behavior in response to stress depend largely on coping strategies, and future research may benefit from efforts to include information on these (45). We included information on a range of potential confounders and outcome-related variables to minimize bias and improve the precision of our estimates. Residual confounding or confounding from other unknown or unmeasured factors may, however, influence our results. Especially somatic risk factors associated with pregnancy complications or maternal disease represent potential sources of confounding for life stress exposures.

In animal studies, maternal gestational stress has been linked to reductions in semen quality (motility, viability, sperm count, and morphology) and testosterone, LH, and FSH levels in offspring (11, 12, 46–48). Further, delayed testicular descent and reduction in anogenital distance and testis size have been observed in rats exposed to prenatal stress (11, 12, 49). Specific changes in testicular tissues include lower diameters of the seminiferous tubules and Leydig cell numbers and higher apoptosis index for germ cells (11, 12, 46, 48). Here, inconsistencies in findings are attributed mainly to differences in the types and intensities of stressors (12, 49). The suggested mechanisms of action for stress exposures during gestation are diverse involving changes in the hypothalamic-pituitary-gonadal axis through alterations in enzyme activity, regulation of various androgen and glucocorticoid receptors, and impulses from direct autonomic innervation of the testicular interstitium (11, 12, 46). While some effects seem to be reversible depending on postnatal stimulation, long-term consequences may, in addition to a diminished reproductive capacity, include changes in the actual response to stress (11, 13). Experimental models of stress exposure in animals mimic several features of conditions in humans reliably (50). However, the complexity of stress in humans is far greater than in nonprimate animals, and our findings do not seem to corroborate a hypothesis of similar patterns in potential effects (51).

Our study must be evaluated in the light of several limitations. We tested a large number of associations on the same data and, hereby, increased the chance of generating statistically significant findings purely by coincidence (52). We have chosen to present results without corrections for potential errors from multiple comparisons. Instead, our findings are interpreted with caution and weighed against existing evidence and a priori hypotheses. Our observed associations between exposure to emotional stress and a higher total sperm count and higher concentrations of estradiol and CFT are not corroborated by previous studies in humans or animals (10–12, 46–48). Further, total sperm count is calculated based on sperm concentration and semen volume, and these measures were not positively associated with emotional stress in our cohort. On the basis of the current lack of biological plausibility, our positive associations may well be random findings. However, we cannot rule out that bias may contribute to these associations or that results, in fact, represent true associations.

Biological samples were collected and analyzed using standardized setups and state-of-the-art techniques validated through both internal and external quality control systems (17). Nonetheless, semen quality outcomes show considerable intraindividual variability when based on semen samples (53). In addition, the secretion of several reproductive hormones is pulsatile following a diurnal cycle (54). While we were able to control for a number of important precision variables related to both semen quality and reproductive hormone levels, we assess all outcomes on the basis of single samples in this study. Although repeated sampling of especially semen is recommendable for clinical diagnoses of infertility, the accuracy of single samples is regarded as sufficient for comparisons of groups of men (55).

The overall participation rate for the F1 generation in our study was rather low (19%). The recruitment process requiring several contacts through a secure digital mailbox system was rather cumbersome and may have discouraged some men from participating. However, we did provide a limited financial compensation for time spent, transportation costs, and inconvenience. In studies requiring semen samples, participation rates below 30% are not uncommon, and selection among participants may introduce bias (53, 56). The young men in the FEPOS cohort were presumably unaware of our selection of exposures to be studied and their own fertility status at enrollment. Thus, bias from selection on these specific characteristics is unlikely. Further, the results were robust to the addition of IPW in a separate model indicating limited bias from selection related to a number of important baseline characteristics. With a highly urban and primarily Caucasian profile, the FEPOS cohort is, however, not entirely representative of young men and stress exposures in Denmark.

On the positive side, our large offspring cohort provided a unique opportunity to study specific long-term health consequences of early life exposures. We combined prospectively collected information from extensive questionnaires, clinical examinations with biological sampling, and high-quality, nationwide registers.

In conclusion, while fetal exposure to maternal psychosocial stress was prevalent among the men in our cohort, we found no indications of negative associations with the measures of reproductive function in young adulthood. This overall message may be particularly reassuring to the many women experiencing common symptoms of stress during pregnancy. Our findings should, however, be viewed in the light of several limitations. The shortened versions of psychometric tools applied in our assessment of maternal stress have not been validated previously among pregnant women, and the resulting relatively low exposure contrast covered the entire span from early pregnancy to the third trimester.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the DNBC. Data can be accessed by permission from the DNBC and the FEPOS research team.

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Exposición fetal al estrés materno y función reproductiva masculina en una cohorte de adultos jóvenes.

Objetivo: Estudiar las asociaciones entre el estrés materno durante el embarazo y la función reproductiva en hombres jóvenes.

Diseño: Estudio de cohorte anidado en una cohorte de nacimientos basada en la población.

Lugar de realización: No aplica.

Paciente (s): hombres jóvenes (n= 1,052; ratio de respuesta, 19%) participando en la cohorte de Programación fetal de calidad del semen desde 2017 a 2019. Fueron reclutados de gestaciones de la Cohorte Nacional de Nacimientos Danesa (1996-2001). Los varones completaron una encuesta online, examen clínico, y recolección de muestras de sangre y semen.

Exposición (es): La información de la vida materna y el estrés emocional estaba disponible de la entrevista telefónica desde el inicio de la gestación hasta aproximadamente la semana 30 de gestación.

Variable principal (es): Aplicamos una regresión negativa binomial, lineal y logística para examinar las asociaciones entre la puntuación de vida, estrés emocional (rango, 0-18) y la función reproductiva. Los resultados primarios fueron medidas de la calidad del semen, y las variables secundarias incluían niveles de hormonas reproductivas y volumen testicular.

Resultados: En general, observamos asociaciones no negativas entre la vida materna o el estrés emocional y la función reproductiva masculina. El estrés emocional materno estaba asociado con mayor recuento total de espermatozoides (16% diferencia; 9% intervalo de confianza [CI], 1-33), estradiol sérico (11% diferencia, 95%CI, 2-21), y el cálculo de testosterona libre ($\beta = 17.8$; 95% CI, 1.26-34.3). Los resultados fueron robustos a la ponderación inversa introducida para tener en cuenta la selección.

Conclusiones: A pesar de que nuestros hallazgos puedan parecer tranquilizadores, son necesarios más esfuerzos para validar las medidas de estrés durante el embarazo y mejorar nuestro conocimiento del amplio espectro de exposiciones a estrés fetal y sus consecuencias para la salud futura más tarde en la vida.