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The Male Disadvantage Hypothesis Reconsidered: Is There Really a Weaker Sex? An Analysis of Gender Differences in Newborn Somatometrics and Vital Parameters

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ABSTRACT The male disadvantage hypothesis was tested based on a data set containing 3518 singleton term births, which took place at a German Clinic for Gynecology and Obstetrics. Gender differences in birth weight, birth length, and head circumference as well as apgar scores were documented and their association patterns with maternal stress parameters were analyzed. As maternal stress the following parameters were defined: nicotine consumption during pregnancy, maternal age younger than 18 years and older than 35 years, maternal prepregnancy weight status (underweight or obese) and pregnancy weight gain of less than 9kg or above 15kg. It could be shown that all maternal stress factors with the exception of low or high pregnancy weight gain reduced the gender differences in newborn somatometrics significantly. Gender differences in the apgar scores were not significantly influenced by maternal stress factors. The results of the present study plead for an increased male vulnerability against stress factors even in utero.

INTRODUCTION

Nearly 40 years ago Richard Naeye introduced the so called "male disadvantage hypothesis" (Naeye et al. 1971), in order to explain the increased risk of perinatal morbidity and morbidity in boys in comparison with girls. Today the newborn male disadvantage is a well established fact. In early spontaneous, chromosomally normal abortions, at least a 30% predominance of male fetuses is described, indicating an effect of X-linked genes acting already in utero (Hassold et al. 1983). Furthermore boys have a slightly increased risk to be affected by congenital maldeformations, show a higher mortality and more postnatal complications as a result of low birth weight, show more often depressed Apgar scores and had a higher frequency of respiratory distress syndrome or lung related injuries and disabilities (Elsmen et al. 2004; Finnstörm 2004). Boys are more often born prematurely and were generally less stable than girls after birth mainly due to pulmonary morbidity but also due to intracranical haemorrhage and urinary tract infections (Stevenson et al. 2000; Thomas et al. 2006). The increased risks for boys seem to continue after perinatal phase and during childhood. Sudden infant death syndrome is more often found among boys than among girls, and even during childhood boys suffer more often from respiratory disease, asthma, gastroenteritis, behaviour disorders, intellectual disability and accidents than girls (Elsmen et al. 2004). Although the male disadvantage hypothesis was proved by many different studies (Stevenson et al. 2000), little is known about possible mechanism contributing to the increased morbidity and mortality in newborn boys. Mainly physiological differences in cerebral blood flow, neonatal stress (Finnström 2004), gender related differences in CSG Levels of IL-8 and antioxidants (Hussein et al. 2007) and gender differences in leptin levels (Pardo et al. 2004) have been discussed as reasons for increased morbidity and mortality in boys. Male fetuses seem to be more vulnerable to an adverse intrauterine environment than female fetuses. Although male newborns are more vulnerable, several studies indicate that male newborns are heavier and longer and exhibit larger head circumferences than their female counterparts (Crawford et al. 1987; Marsal et al. 1996; Yankova 2005). According to the male disadvantage hypothesis however we may hypothesize that maternal stress factors during pregnancy may have an

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increased adverse effect on fetal growth in males in comparison to females. The aim of the present study was to test the hypothesis that maternal stress factors result in a decrease in gender differences somatometrics and vital parameters. We defined following stress factors: maternal age (below 18 years and above 35 years), nicotine consumption during pregnancy, prepregnancy weight status (underweight, overweight or obese) and pregnancy weight gain (below 9kg or above 15kg).

METHODOLOGY

Data Set

The present study is based on a data set of 3518 singleton births which took place at the Clinic for Gynecology and Obstetrics of Westerstede-Ammerland, Germany between 1990 and 1995. In our study we included the data of 3455 primiparae women ageing between 16 and 44 years (x=28.4; SD=4.5) at the time of giving first birth. We used the following inclusion criteria: term birth between the 38 and 42th week of gestation, all recommended prenatal check ups (n=8) were completed, the delivery of single infants without congenital maldeformations, no registered maternal diseases before and during pregnancy, no hypertension (BP < 150/90 mmHg), no protein or glucose in the urine, no pregnancy related immunization. Furthermore coincident medical diseases such as diabetes mellitus or nephropathy, drug or alcohol abuse and twin birth or IVF were strict exclusion criterions. Gestational age was calculated in terms of the number of weeks from the beginning of the last menstrual bleeding to the date of delivery (= duration of amenorrhoea) and by two consecutive ultrasound examinations performed before the 12th week of gestation. All probands (mothers) were of German origin. Regarding social class it could be stated that our sample contained predominantly middle class women living in Westerstede-Ammerland and the surrounding rural areas. All had finished school, or were at school (especially the adolescent mothers in the sample) at the time of pregnancy.

Newborn Features

One and five minute APGAR Scores for evaluation of the newborn (Jonnett et al. 1981; Forsblad et al. 2007) were determined and all newborns were measured immediately after birth. The following parameters were taken directly from the newborn: Birth weight, birth length, head circumference. Birth weight status was defined according to the recommendations of the WHO (1980): a low birth weight as defined as < 2500g, a normal birth weight as 2500- 4000g and a macrosomia as a birth weight > 4000g.

Maternal Features

Beside the documentation of nicotine consumption the following somatometric data of all women were documented: Stature, prepregnancy weight (PPW), prepregnancy weight status (BMI), weight at the end of pregnancy (EPW) and weight gain during pregnancy (PWG). Stature was determined at the first prenatal visit. Prepregnancy weight was estimated by means of the retrospective method and the first weight determination, which was carried out at the first prenatal visit (8th week of gestation). In order to determine prepregnancy weight the mean value of the retrospective estimated weight and the weight at the 8th week of gestation was calculated. Weight status was estimated by means of Body mass index, BMI (Body weight/Stature^2). All somatometric features were determined according to the recommendations of Knussmann (1988) and Pschyrembel (1976).

Maternal Stress Parameters

The following parameters were chosen as maternal stress parameters which might affect newborn characteristics: Maternal age at birth, nicotine consumption, pregnancy weight gain and maternal prepregnancy weight status.

Statistical Analysis

Statistical analyses were performed by means of SPSS for Windows Program Version 16.0 (Microsoft corp.). After calculation descriptive statistics (means, SDs) group differences were tested regarding their statistical significance using student t- tests, and one way ANOVAS (duncan tests). Crosstabs (Chi-squares) were calculated to test frequency differences with respect to their statistical significance. Multiple regression analyses were computed in order to test the impact of maternal age and maternal somatic characteristics on newborn weight.

RESULTS

Maternal and Newborn Characteristics

Maternal and newborn characteristics are presented in tables 1 and 2. As to be seen mean maternal age at the first birth (x= 28.4 years) corresponded to the typical age of European primiparae. The majority of women were classified normal weight (62.7%) according to the definition of the WHO. More than 50% of the women gained weight 9 and 15 kg during the course of pregnancy. Only 17.7% of the women smoked during pregnancy. Regarding the newborns it could be shown than girls and boys differed statistically significantly in birth weight, birth length and head circumferences, while no significant gender differences in the Apgar scores could be observed. Weight status at birth corresponded in more than 98% with the WHO definitions of normal weight or macrosomia. Only 1.9% of the girls and 0.8% of the boys were classified as low birth weight newborn with a weight below 2500g. Concerning maternal risk factors it turned out: 17.7% of the mothers smoked during pregnancy, 0.5% of the mothers were younger than 18 years when giving first birth, 6.6% were older than 35 years at the time of first birth, 2.8% were underweight during prepregnancy phase while 10.3% were obese during prepregnancy phase. 20.1% experienced a pregnancy weight of less than 9kg, 23.3% gained more than 15kg.

Table 1: Maternal characteristics (x, SD, %)

Maternal characteristics	*% , x (SD)*
Age (yr)	28.4
Age groups	
<18yr	0.5%
18-29yr	60.9%
30-34 yr	32%
> 35 yr	6.6%
Stature height (cm)	168.3 (6.5)
Prepregancy weight (PPW)	68.7 (13.1)
Prepregnancy Weight Status (BMI)	
Under weight BMI < 18.50	2.8%
Normal weight BMI 18.50-24.99	62.7%
Overweight BMI 25.00-29.99	24.1%
Obese BMI > 30.00	10.3%
End of pregnancy weight (EPW)	81.2 (13.3)
Pregnancy weight gain	12.3 (4.7)
< 9kg	20.1%
9-12kg	32.6%
13-15kg	24.0%
>15kg	23.3%
Nicotine Consumption	
Non smoker	82.3%
smoker	17.7%
Number of cigarettes / d	8.3 (6.4)

Maternal Impact on Newborn Somatometrics

Newborn somatometrics was significantly related to several maternal parameters such as maternal age, prepregnancy weight status, pregnancy weight gain and nicotine consumption. As to be seen in table 3 according to the results of the multiple regression analyses with increasing maternal age, prepregancy weight status and pregnancy weight gain, birth weight, birth length and head circumference increased significantly. This was true of both genders

As to be seen in table 3 nearly all maternal stress factors, i.e. maternal age, prepregnancy weight status, pregnancy weight gain and nicotine consumption had a significant impact on newborn somatometrics. Newborn dimensions increased with increasing maternal age, increasing weight gain and increasing prepregnancy weight status. Nicotine consumption, however, has the opposite effect.

Gender Differences in Newborn Characteristics and Maternal Stress Parameters

In table 4 gender differences in newborn

Table 2: Newborn characteristics according to newborn sex

	Female *X (SD)*	*Male* *X (SD)*	*Sig (p)*
Birth weight	3482.7 (471.9)	3625.7 (481.3)	<0.001
Birth length	52.5 (2.5)	53.3 (2.5)	<0.001
Head circumference	34.9 (1.3)	35.6 (1.4)	<0.001
Apgar score 1 minute	8.7 (0.9)	8.6 (0.9)	n.s.
Apgar score 5 minutes	9.7 (0.7)	9.6 (0.8)	n.s.
Weight Status			
Low birth weight < 2500g	1.9%	0.8%	<0.001
Normal weight 2500-4000g	85.1%	77.8%	
Macrosomia > 4000g	13.0%	21.3%	

somatometrics and Apgar scores according to maternal stress factors are presented. Regarding the stress parameter maternal nicotine consumption it could be shown, that the mean gender differences in birthweight, birth length and head circumference were significantly lower among smoking mothers. Maternal age had also a significant effect on gender differences. Highest mean gender differences in birth weight were found among mothers ageing between 18 and 30 years. Among mothers younger than 18 years, female newborns were heavier and longer and exhibited a higher head circumference. Regarding pregnancy weight gain it turned out, that gender differences in birth weight were highest among mothers gaining weight between 13 and 15kg during pregnancy. Gender differences in birth weight were also associated with maternal prepregnancy weight status. Maternal underweight resulted in the significantly lowest gender differences in birth weight, maternal normal weight was associated with the highest gender difference gender differences in birth weight. Maternal stress parameters had also an important impact on gender differences in the prevalence of low birth weight (<2500g). As to be seen in figure 1 the percentage of low weight male newborns was 4 times higher among smoking mothers in comparison to non smoking mothers. Among girls however, the percentage of low weight newborns was less than twice as high among smoking mothers in comparison to their non smoking counterparts ($p < 0.01$). Regarding maternal prepregnancy weight status it turned out, that the gender difference in the prevalence of low weight newborns was highest among normal weight mothers ($p < 0.05$) (see Fig. 2). Maternal age was also significantly related ($p < 0.01$) with

Table 3: Impact of maternal parameters on newborn size; multiple regression analyses

Dependent variable: Birthweight	R^2	*Coefficient*	*Sig*	*95% confidence interval*
Female				
Maternal age	0.12	7.8	<0.002	2.99 - 12.67
Prepregancy weight status		24.9	<0.001	19.95 - 29.89
Weight gain		20.9	<0.001	16.42 - 25.51
Nicotine consumption		-14.1	<0.001	-19.08 - -9.05
Male				
Maternal age	0.09	7.4	<0.003	2.57 - 12.16
Prepregancy weight status		20.5	<0.001	15.27 - 25.73
Weight gain		21.7	<0.001	17.03 - 26.36
Nicotine consumption		-15.7	<0.001	-21.13 - -10.35
Dependent variable: Birth length	R^2	*Coefficient*	*Sig*	*95% confidence interval*
Female				
Maternal age	0.06	0.04	<0.002	0.01 - 0.07
Prepregancy weight status		0.09	<0.001	0.07 - 0.12
Weight gain		0.08	<0.001	0.06 - 0.11
Nicotine consumption		-0.06	<0.001	-0.08 - -0.03
Male				
Maternal age	0.06	0.04	<0.001	0.02 - 0.07
Prepregancy weight status		0.09	<0.001	0.06 - 0.11
Weight gain		0.08	<0.001	0.06 - 0.11
Nicotine consumption		-0.07	<0.001	-0.11 - -0.05
Dependent variable: Head circumference	R^2	*Coefficient*	*Sig*	*95% confidence interval*
Female				
Maternal age	0.06	0.01	n.s.	-0.01 - 0.02
Prepregancy weight status		0.05	<0.001	0.04 - 0.07
Weight gain		0.05	<0.001	0.04 - 0.07
Nicotine consumption		-0.02	<0.002	-0.04 - -0.01
Male				
Maternal age	0.05	0.02	<0.005	0.01 - 0.03
Prepregancy weight status		0.05	<0.001	0.04 - 0.07
Weight gain		0.05	<0.001	0.03 - 0.06
Nicotine consumption		-0.03	<0.001	-0.04 - -0.01

Table 4: Gender differences in newborn features according to maternal age, nicotine consumption, prepregnancy weight status and pregnancy weight

	Birth weight (in g)			Birth length (in cm)			Head circumference (in cm)			APGAR 1			APGAR 5		
	Female x (SD)	*Male x (SD)*	*Diff*	*Female x (SD)*	*Male x (SD)*	*Diff*	*Female x (SD)*	*Male x (SD)*	*Diff*	*Female x (SD)*	*Male x (SD)*	*Diff*	*Female x (SD)*	*Male x (SD)*	*Diff*
Nicotine Consumption															
Smoker	3339.6 (462.8)	3478.2 (492.3)	138.5	51.8 (2.4)	52.6 (2.5)	0.7	34.7 (1.4)	35.3 (1.4)	0.5	8.7 (0.8)	8.6 (0.8)	-0.1	9.7 (0.6)	9.6 (0.7)	-0.1
Non smoker	3512.1 (468.5)	3659.1 (472.6)	147.0	52.7 (2.5)	53.5 (2.5)	0.8	35.1 (1.3)	35.7 (1.4)	0.7	8.7 (0.9)	8.6 (0.9)	-0.1	9.7 (0.8)	9.6 (0.9)	-0.1
Sig (p)		<0.001			<0.01			<0.01			n.s.			n.s.	
Maternal Age Group															
< 18 a	3527.5 (581.1)	3501.1 (282.8)	-27.5	53.8 (3.3)	52.5 (3.5)	-1.3	35.8 (0.9)	34.5 (2.1)	-1.3	8.5 (0.6)	9.0 (0.4)	0.5	9.5 (0.6)	9.8 (0.4)	0.5
18-30a	3461.5 (475.3)	3613.2 (474.7)	151.7	52.4 (2.5)	53.3 (2.5)	0.9	34.9 (1.4)	35.6 (1.4)	0.6	8.7 (0.9)	8.6 (0.9)	-0.1	9.7 (0.8)	9.6 (0.8)	-0.1
31-35a	3515.8 (465.2)	3643.2 (474.6)	127.4	52.7 (2.4)	53.4 (2.4)	0.7	35.0 (1.3)	35.7 (1.4)	0.6	8.7 (0.8)	8.7 (0.8)	-0.1	9.7 (0.7)	9.7 (0.8)	-0.1
> 35a	3524.3 (462.5)	3654.2 (573.4)	129.9	52.7 (2.3)	53.7 (2.9)	1.1	35.0 (1.4)	35.8 (1.3)	0.7	8.8 (0.7)	8.6 (1.3)	-0.2	9.7 (0.6)	9.5 (1.4)	-0.2
Sig (p)		<0.05			<0.01			<0.001			n.s.			n.s.	
Pregnancy Weight Gain (PWG)															
< 9kg	3367.4 (486.9)	3487.6 (461.7)	120.2	52.0 (2.6)	52.9 (2.5)	0.9	34.7 (1.3)	35.4 (1.3)	0.7	8.7 (0.9)	8.7 (0.8)	-0.1	9.7 (0.8)	9.6 (0.7)	-0.1
9-12kg	3468.4 (447.3)	3568.8 (460.9)	100.4	52.4 (3.3)	53.1 (2.5)	0.7	34.9 (1.3)	35.6 (1.4)	0.6	8.7 (0.8)	8.7 (0.9)	0.1	9.7 (0.6)	9.7 (0.9)	-0.1
13-15kg	3492.3 (455.3)	3672.3 (506.8)	180.1	52.7 (2.4)	53.5 (2.5)	0.7	35.0 (1.3)	35.7 (1.4)	0.6	8.7 (0.8)	8.6 (0.9)	-0.1	9.7 (0.8)	9.6 (0.9)	-0.1
> 15kg	3607.6 (479.5)	3758.9 (457.5)	151.2	52.9 (2.5)	53.8 (2.4)	0.9	35.3 (1.4)	35.9 (1.4)	0.6	8.7 (0.9)	8.5 (0.9)	-0.1	9.7 (0.7)	9.6 (0.8)	-0.1
Sig (p)		<0.001			<0.01			n.s.			n.s.			n.s.	
Maternal Prepregnancy Weight Status (BMI)															
< 18.50	3253 (453.9)	3305.9 (347.8)	52.8	51.6 (2.5)	51.6 (2.1)	0.0	34.5 (1.4)	34.9 (1.1)	0.3	8.8 (0.6)	8.8 (0.6)	0.0	9.7 (0.6)	0.8 (0.4)	0.1
18.50-24.99	3443.9 (453.9)	478.8 (478.8)	158.8	52.4 (2.4)	53.2 (2.4)	0.9	34.9 (1.3)	35.6 (1.4)	0.6	8.7 (0.8)	8.7 (0.9)	-0.1	9.7 (0.7)	9.6 (0.8)	-0.1
25.00-29.99	3535.7 (496.5)	3676.3 (478.3)	140.6	52.8 (2.7)	53.6 (2.6)	0.8	35.1 (1.4)	35.8 (1.3)	0.7	8.7 (0.9)	8.6 (0.9)	-0.1	9.7 (0.8)	9.6 (0.8)	-0.1
> 30	3646.1 (473.3)	3760.1 (477.1)	114.1	53.1 (2.2)	53.8 (2.5)	0.7	35.3 (1.4)	35.9 (1.3)	0.6	8.6 (1.2)	8.5 (1.1)	-0.1	9.6 (1.1)	9.5 (1.2)	-0.1
Sig (p)		<0.01			<0.01			<0.05			n.s.			n.s.	

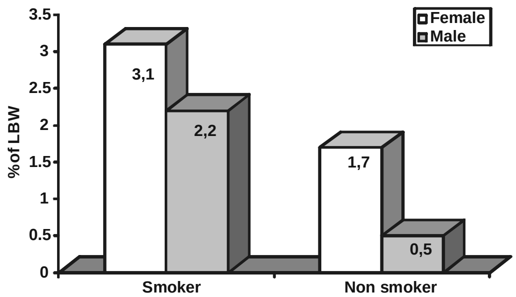

Fig. 1. Percentage of LBW (< 2500g) newborns according to sex and maternal nicotine consumption

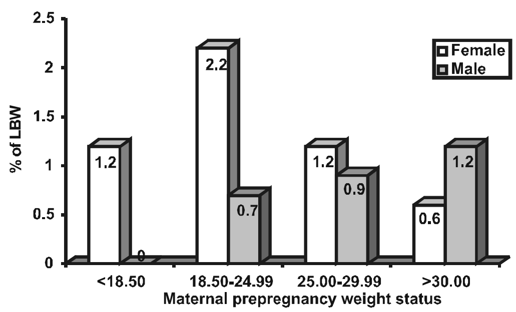

Fig. 2. Percentage of LBW (< 2500g) newborns according to sex and maternal prepregnancy weight status

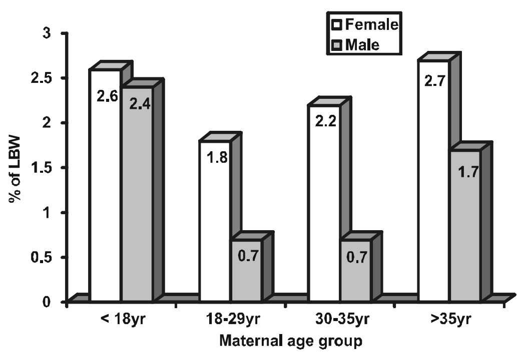

Fig. 3. Percentage of LBW (< 2500g) newborns according to sex and maternal age group

gender differences in the prevalence of low birth weight. The lowest gender differences were found among mothers ageing between 18 and 35 years (see Fig. 3). No significant association between gender differences in low birth weight and pregnancy weight gain could be stated.

DISCUSSION

Males exhibit higher mortality than females at every age nearly worldwide (Yu 2003; Ogbolu 2007; Jehan et al. 2009). These gender differences begin in utero, when gonadal steroid production already differs markedly between male and female fetuses (Drevenstedt et al. 2008). It is well documented that males are more likely to be born prematurely and to suffer more frequently from respiratory stress syndromes and infectious diseases than females in the perinatal period (Elsmen et al. 2004; Thomas et al. 2006; Drevenstedt et al. 2008). Since the early seventies of the 20th century these gender differences in morbidity and mortality are explained by the "male disadvantage hypothesis" (Naeye et al. 1971).According to this hypothesis boys are the weaker sex, reacting more sensitive to adverse environmental factors during gestation, infancy and childhood (Naeye et al. 1971; Cagnacci et al. 2003, Shinwell et al. 2007). This male disadvantage can also be transferred from boys to girls in unlike-sex twin pairs, may be via an intrauterine paracrine effect (Shinwell et al. 2007; Stevenson and Tyson 2007). This sex-biased environmental sensitivity is not unique among humans, it was also found among other mammalians such as sheeps (Bennet et al. 2007) but also among birds (Kalmbach et al. 2005). In the present paper another aspect of the male disadvantage hypothesis was tested: It is well documented that newborn girls and boys differ significantly in somatometric dimensions (Crawford et al. 1987; Marsal et al. 1996; Elsmen et al 2004; Yankova 2005).These gender differences in newborn dimensions are also found among non-human primates (Joffe et al. 2005; Geary et al. 2003). In general newborn boys are heavier and longer, and exhibit a higher head circumference than newborn girls, although girls in contrast exhibit a higher amount of subcutaneous fat distribution (Rodriguez et al. 2004). We hypothesized that maternal stress factors during gestation reduce somatometric gender differences in newborns. The results of the present study corroborate this idea. Especially birth weight was affected by maternal stress factors. It turned out that maternal nicotine consumption during pregnancy reduced the gender differences in birth weight, birth length and head circumference significantly in comparison to the gender differences among non smoking mothers. These results are in accordance with the male disadvantage hypothesis. Smoking during pregnancy is an important stress factor because it retains fetal growth through placental vascular effects and via associated effects on leptin metabolism (Coutant et al. 2001; Kayemba-Kay´s et al. 2008). Leptin concentration is positively correlated with birth weight and birth length and leptin levels differ between the male and female newborns (Pardo et al. 2004). Girls show per se higher leptin levels than boys and therefore an impaired leptin production caused by maternal nicotine consumption may affect male fetuses to a higher degree. Nevertheless the results of the present study are in contradiction of those of Voigt et al. (2006) who described an adverse effect of maternal smoking on birth weight of girls but not on newborn weight of boys. Beside nicotine consumption in the present study maternal age was considered as an important maternal stress factor. Especially a low maternal age below 18 years and a high maternal age above 35 years are considered as risky (Newcomb et al. 1991; Milner et al. 1992; Fraser et al. 1995; Storbino et al. 1995; Plöckinger et al. 1996; Botting et al. 1998; Lao and Ho 1998). The results of the present study are in accordance with this assumption. The significantly highest gender differences in birth weight were found among the newborns of mothers ageing between 18 and 30 years. Among this maternal age group boys showed the highest advantage in birth weight in comparison with their female counterparts. Furthermore the stress factors maternal prepregnancy weight status and pregnancy weight gain were associated with gender differences in birth weight. The significantly highest gender differences in birth weight were found among normal weight mothers and among mother who experienced a weight gain between 13 and 15 kg. The lowest gender difference in birth weight was found among underweight women. The effects of maternal prepregnancy weight status and pregnancy weight gain on newborn size in general are well known (Kirchengast and Hartmann 1998), the gender typical differences of the impact of maternal weight status and pregnancy weight gain on newborn somatometrics however, corroborates the male disadvantage hypothesis. From a physiological point of view these results may be explained by a sex-biased environmental sensitivity caused by gender typical differences in leptin levels and general hormonal function. Boys grow faster and have a higher metabolic rate than girls during gestation, however when oxygen is limited they might deplete available resources more rapidly (Bennet et al. 2007). But what are the ultimate reasons for these gender typical differences in vulnerability? As biologists we have also to consider an evolutionary explanation too: From an evolutionary point of view gender differences in early vulnerability may be attributed to the natural selection of optimal maternal strategies to maximize life time reproductive success (Wells 2000; Lummaa et al. 2001; Lummaa and Clottonn-Brock 2002; Beise and Voland 2002). Wells tried to explain the increased male sensitivity to adverse environmental conditions using the Trivers-Willard hypothesis of differential parental investment (Trivers and Willard 1973). According to this hypothesis in vertebrates in general nearly all females mate successfully, while male reproductive success is only ensured under good environmental conditions. Trivers and Willard concluded that parents, especially mothers, manipulate the sex ratio of their offspring according environmental conditions. According to Wells (2000) natural selection is predicted to favour increased male vulnerability to general factors such as infectious diseases or malnutrition because of its role on optimizing maternal reproductive fitness.

CONCLUSION

The results of the present study plead for an increased male vulnerability to maternal stress factors such as nicotine consumption during pregnancy, too low or too high maternal weight status and maternal age.

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