RBMO

ELSEVIER

ARTICLE

Birth characteristics in men with infertility

BIOGRAPHY

Gunilla Sydsjö is Professor at the Faculty of Health Sciences, Linköping University, and Certified Cognitive Behaviour Therapist, Department of Obstetrics and Gynaecology, University Hospital of Linköping. Her research focus is bio-psychosocial risks for women and children, reproduction, infertility, women's mental and somatic health, and short- and long-term outcomes for children.

Susanne Liffner*, Elizabeth Nedstrand, Marie Bladh, Heriberto Rodriguez-Martinez, Mats Hammar, Gunilla Sydsjö

KEY MESSAGE

Men with restricted intrauterine growth may be at risk of male factor infertility in adulthood. Men with male infertility factor had a higher prevalence of non-optimal birth characteristics than the reference group.

ABSTRACT

Research question: Are low birth weight, prematurity, being born small for gestational age, or both, associated with a higher risk of male factor infertility in adulthood?

Design: Retrospective study of a clinical sample of 892 men, diagnosed with an infertility factor (male, female, combined or unexplained) together with their female partner at a University Hospital clinic in Sweden between 2005 and 2010. Data on birth weight and gestational age at birth were retrieved from the Swedish Medical Birth Register. The distribution of non-optimal birth characteristics in relation to infertility factor was described. A control group was created consisting of two men for each index man, born in Sweden in the same year as each index men, as well as a reference group consisting of all men born in Sweden the same years.

Results: The likelihood of having been born small for gestational age was almost fivefold higher in men with male factor infertility than in men with unexplained infertility (OR 4.84, 95% CI 1.32 to 17.80). Men with male factor infertility were more often born with non-optimal birth characteristics than the control group (14.8% versus 8.5%; $P = 0.010$) and the reference group (14.8% versus 11.4%; $P < 0.001$). Men with azoospermia were more often born with non-optimal birth characteristics, compared with men without azoospermia (21.3% versus 12.1%; $P = 0.038$).

Conclusions: The results suggest an association between intrauterine growth restriction and male factor infertility in adulthood.

Obstetrics and Gynaecology, Department of Biomedical and Clinical Sciences, Faculty of Medicine and Health Sciences, Linköping University, Linköping SE-581 85, Sweden

*Corresponding author. E-mail address: Susanne.liffner@liu.se (S Liffner). https://doi.org/10.1016/j.rbmo.2020.04.026 1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

KEYWORDS

IVF
low birth weight
male factor infertility
preterm birth
small for gestational age

INTRODUCTION

It is well known that preterm birth (PTB) defined as birth before gestational week 37 (*Keller et al., 2010*) and restricted fetal growth, represented by variables such as small for gestational age (SGA) (defined as a birth weight less than –2 SD of the mean weight for the gestational length) (*Marsal, 1996*), low birth weight (LBW) (defined as birth weight <2500 g), or both, can increase the risk of diseases later in life, e.g. those inherent to the metabolic syndrome (*Barker et al., 1993*; *Barker, 1998*; *Hodgson and Coe, 2005*; *McMillen and Robinson, 2005*). According to a Swedish population-based study (*deKeyser et al., 2012*), men born preterm, SGA or with LBW, were also less likely to reproduce than those with normal birth characteristics. Being born large for gestational age (LGA) (defined as birthweight over +2 SD of the mean weight for the gestational age) has not been shown to affect future reproduction (*deKeyser et al., 2012*). In a previous study using Swedish national registers (*Liffner et al., 2017*), it was found that men who became fathers after intracytoplasmic sperm injection (ICSI) were more often born SGA than men who became fathers after conventional IVF, suggesting that restricted intrauterine growth increases the risk of male infertility.

Although these data on non-optimal birth characteristics (used as a grouping-term for PTB, LBW and SGA) are risk factors for lower reproductive rate, it is still uncertain whether birth weight is associated with semen quality or with other causes of subfertility. Sperm parameters did not seem to be related to birth weight when analysing semen samples from men without a diagnosis of infertility (*Ramlau-Hansen et al., 2010*; *Whitcomb et al., 2017*). In a study of men with unexplained infertility, all born at term with normal birth weight (>2500 g), birth weight was inversely correlated to total sperm count and positively correlated to sperm fragmentation (*Faure et al., 2015*). In another study, the proportion of infertile men born with LBW was higher than for fertile men (*Boeri et al., 2016*). Also, sperm motility and morphology were lower for infertile men born LBW than for infertile men born with normal or high birth weight (*Boeri et al., 2016*). On the other hand, a registry study from 2001 (*Ozturk et al., 2001*) found no association between LBW and male infertility (diagnosed using World Health Organization criteria [WHO] from 1999, when the cut-off levels for a normal semen sample were higher). If the fetus is exposed to an unfavourable environment, the risk of altered development of genital organs increases, which might affect reproductive function (*Francois et al., 1997*; *Cicognani et al., 2002*; *Main et al., 2006*; *Faure et al., 2015*).

The aim of the present study was to describe the birth characteristics of male partners in couples with infertility. The hypothesis being tested is that non-optimal birth characteristics, in this study represented by LBW, PTB and SGA, are associated with a higher risk for male-factor infertility in adulthood. Results of assisted reproductive technique (ART) interventions are explored to compare men with or without non-optimal birth characteristics and men with different infertility factors.

MATERIAL AND METHODS

Participants

All men participating in this study were male partners in couples who, after clinical assessment, were accepted for infertility intervention at the Reproductive Medicine Centre (RMC), University Hospital, Linköping, Sweden, between 2005 and 2010. Their female partners have been studied and reported previously (*Vikstrom et al., 2014*). At the start, 1152 men were identified and 1070 provided written consent to access information from their medical charts as well as from the Swedish Medical Birth Register (MBR) (*National Board of Health and Welfare 2003*; *2009*), a national register created in 1973. A total of 926 of these men were identified in the MBR, using the unique personal identification number assigned to each person residing in Sweden. Men not identified in the MBR (n = 144) were either born outside of Sweden or before 1973. The final study sample consisted of 892 men, as information on birth weight, gestational age, or both, was missing in 34 cases. A total of 350 men had either been diagnosed with azoospermia (n = 61) or had not undergone any infertility intervention (n = 289) and were thus excluded from analyses pertaining to treatment. Men with azoospermia who had undergone sterilization were not included in the study.

To evaluate the distributions of the birth characteristics in the study population, information on birth characteristics on all men born during the same period were retrieved from the MBR (n = 538,839). These men are referred to as the reference group. In addition, from these MBR data, a control group of two men were matched on year of birth to each of the index men (n =1784). The birth characteristics of the men in the control group and the reference group were compared with birth characteristics for men diagnosed with infertility at RMC. Men in the study group were excluded from the reference group material but it was not possible to exclude men with undiagnosed male factor infertility.

Infertility treatment at Reproductive Medicine Centre, Linköping University Hospital

Couples experiencing infertility according to the WHO criteria (*Zegers-Hochschild et al., 2009*) and residing in the south east healthcare region of Sweden can be referred to RMC for infertility intervention. The region has a large rural area but also urban areas in which the three largest cities combined had around 380,000 inhabitants at the time of the study.

Most of the ART cycles carried out at RMC were publicly funded. Couples must fulfil certain conditions to become entitled to publicly funded treatments. These conditions are the results of political decisions and therefore change over time. At the time of the study, the conditions included female age younger than 38 years, male age younger than 55 years and female body mass index (BMI) below 30. No serious medical condition that could be worsened by a pregnancy was allowed. Only two embryo transfers were publicly funded, fresh or frozen thawed. Couples who had not conceived after two embryo transfers were allowed to continue with privately financed treatments.

Couples accepted for ART intervention were asked to complete a health questionnaire that contained questions on age, marital status (married/co-habiting), height and weight, smoking and snuff habits (yes/no), chronic illnesses, and regular intake of medication and allergies. All men and their partners underwent a medical investigation aiming to find the cause of infertility, which for the men included spermiogram

screening. All spermiograms from men who initially were diagnosed with male or combined infertility were re-assessed according to WHO standards from 2010 (semen volume >1.5 ml, total sperm count >39 million, sperm concentration >15 million/ml, progressive motile >32%, total motile >40%, normal morphology >4%) (*Cooper et al., 2010*). If the first semen sample was normal according to previously mentioned WHO criteria, this was considered sufficient. In the case of azoospermia or severe oligozoospermia (<5 million/ml), an extended examination was conducted, including hormonal screening and karyotyping.

Their female partners went through a gynaecologic examination and ultrasound scanning, including tests for fallopian tube patency. The physician conducting the infertility investigation of the couple then determined the factor of infertility.

Female factor infertility included tubal occlusion, anovulation and ovarian insufficiency according to clinical routine. Men were diagnosed with male factor infertility when two or more semen analyses had shown sperm parameters below the normal range (*Cooper et al., 2010*). When both a male and a female factor were present, the term combined infertility was used. When no factor was found, the infertility was categorized as unexplained.

Data collection

Information on type of infertility (female, male, combined or unexplained), smoking and snuff habits (yes/no) and weight and height was retrieved from medical charts and from the questionnaires completed by patients. All spermiograms from men who were initially diagnosed with male or combined infertility have been re-assessed and re-diagnosed according to WHO standards from 2010, before statistical analyses were carried out. The patient's body mass index (BMI) was calculated from the height and weight and divided into four categories (underweight <18.5 kg/m^2; normal range 18.5–24.99 kg/m^2; overweight 25.00–29.99 kg/m^2; and obese ≥30.00 kg/m^2) (*WHO, 2000*).

To be able to study the results of the treatments, i.e. ART method used, pregnancy rate and number of interventions, the study was closed in March 2016 when the couples had been through all their treatment cycles. This includes using all their frozen embryos.

Birth characteristics of the male patients and controls were retrieved from the national MBR, which includes information on 97–99% of pregnancies that have resulted in deliveries in Sweden since 1973. The register contains information about the pregnancy, delivery and antenatal health of the child and is based on the medical charts from maternal health care, obstetric care as well as infant care (*National Board of Health and Welfare 2003*; *2009*). The information retrieved included height, weight and gestational week at birth. When birth characteristics are described in the present study, the birth characteristics of the male partner and not of the offspring are referred to.

Ethics

The study was approved by the Regional Ethical Review Board in Linköping, 03-556, 07-M66 08–08-M 233-8, 2014-112/31 on 26 March 2014.

Statistical analyses

The distribution of BMI, LBW, SGA, LGA, PTB and any non-optimal birth characteristic (either LBW, SGA, LGA or PTB, which are not mutually exclusive birth characteristics) divided by the number of individuals in the categories female, male, combined or unexplained infertility were calculated. Chi-squared tests were used to determine any differences between the category groups. The analyses were two sided and the default significance level was set at $P < 0.05$. Because of multiple testing, however, the *P*-values were adjusted using Bonferroni's correction and the *P*-values from these adjustments are presented in the tables. The male and combined categories were added together to form a separate category to include all men diagnosed with a male factor contributing to infertility in the same category. The distribution of the above-mentioned variables was also calculated for this category.

Single logistic regression analyses were used to study differences between the categories of diagnosed infertile men (male factor or combined, female factor or unexplained) against PTB, LBW or SGA. Multiple logistic regression was used to compare men with male or combined infertility with those with female or unexplained infertility against the above-mentioned birth characteristics, including adjustment for BMI and tobacco consumption habits. All analyses were carried out using IBM SPSS version 22 (Armonk, NY, USA).

RESULTS

The sample of men included had 1976 as the median birth year (range 1973 to 1986) and thus were between 29 and 37 years old at the time of inclusion. The median year of birth for men with different infertility factors were 1975 (unexplained) and 1976 (male, female and combined). Their partners were on average one year younger (median year of birth for women with different infertility factors were 1976 (unexplained), 1977 (male and female) and 1978 (combined). Infertility related to female causes accounted for 33.3% of the cases, male causes for 20.4%, combined causes for 22.2% and those remaining unexplained accounted for 24.1% of the cases (TABLE 1). The BMI was normal in 47.4% of the men (BMI 18.5–24.99 kg/m^2), whereas 52.0% were overweight or obese (BMI ≥30.00 kg/m^2) and 0.6 % underweight (BMI <18.5 kg/m^2) (TABLE 1). No significant differences were found between the groups of men divided by infertility type in BMI or smoking habits, but men with male or combined factor infertility used snuff less often ($P = 0.040$) (TABLE 1).

The proportion of men born with PTB, LBW or SGA stratified according to their infertility diagnosis is presented in TABLE 2. Men with male factor infertility were more often born with non-optimal birth characteristics than men in the control group (14.8% compared with 8.5%; $P = 0.010$). The proportion of men with non-optimal birth characteristics in the reference group, was 11.4% ($P < 0.001$). When excluding men born LGA from the group of men born with non-optimal birth characteristics, 12.1% of men with male factor were born PTB, SGA or with LBW compared with 8.2% in the control group ($P = 0.077$) or 8.8% in the reference group ($P = 0.0042$). The proportion of men with PTB, LGA and LBW was similar in all groups with different infertility factors. Out of the men born SGA or born with LBW, 55.2% (21/38) and 52.9% (18/34), respectively, had male or combined factor.

The likelihood of being born SGA was almost fivefold higher for men with

TABLE 1 DISTRIBUTION OF BODY MASS INDEX AND USE OF TOBACCO AMONG INDEX MEN BY DIAGNOSED FACTOR OF INFERTILITY

Variable	Diagnosed factor of infertility								Total		*P*-value[a]
	Unexplained		Female		Male		Combined				
	n	%	*N*	%	*n*	%	*n*	%	*n*	%	
Infertility type	215	24.1	297	33.3	182	20.4	198	22.2	892	100.0	
BMI											1.000
<18.5	1	0.5	1	0.4	2	1.2	1	0.6	5	0.6	
18.5–24.99	90	47.4	117	43.8	85	52.5	87	48.1	379	47.4	
25–29.99	85	44.7	120	44.9	56	34.6	75	41.4	336	42.0	
>30	14	7.4	29	10.9	19	11.7	18	9.9	80	10.0	
Missing	25		30		20		17		92		
Habitual smoker											
Yes	13	6.7	12	4.2	10	5.8	9	4.6	44	5.2	1.000
No	182	93.3	272	95.8	161	94.2	185	95.4	800	94.8	
Missing	20		13		11		4		48		
Habitual use of snuff											
Yes	62	31.8	82	28.9	34	19.9	39	20.2	217	25.7	0.040
No	133	68.2	202	71.1	137	80.1	154	79.8	626	74.3	
Missing	20		13		11		5		49		

[a] Significance level $P < 0.05$; Bonferroni adjusted *P*-values from Pearson's chi-squared test.

male factor infertility than for men with unexplained infertility, OR 4.84 (95% CI 1.32 to 17.80; $P = 0.018$), when adjusted for BMI and smoking (TABLE 3). The unadjusted OR for being born SGA for men with male infertility was 3.05 (95% CI 1.05 to 8.23; $P = 0.040$), and OR with adjustment for BMI alone was 4.84 (95% CI 1.32 to 17.76; $P = 0.017$). Men with male or combined infertility also seemed to have an increased likelihood of being born SGA or with LBW compared with men in couples with female factor infertility but the sample size in this analysis was too small to establish a significant difference.

To further elucidate the effect of non-optimal birth characteristics on male infertility, subgroup analyses of men with and without azoospermia was carried out. These analyses showed that 21.3% of the men with azoospermia were born with non-optimal birth characteristics compared with 12.1% of the men without azoospermia ($P = 0.038$). Men with azoospermia also seemed more likely to be born SGA or with a LBW, although these differences did not reach statistical significance (data not shown).

Men with male or combined cause of infertility were, as expected, more often treated with ICSI than men in couples with other infertility diagnoses (TABLE 4). No statistically significant difference was found in treatment outcome between the different infertility factors (TABLE 4). Being born with non-optimal birth characteristics did not affect the chance of conceiving after ART. Rates of either pregnancy or live birth were also similar between groups (data not shown).

DISCUSSION

In this study, men with male factor infertility were more often born SGA compared with men with unexplained infertility. Men with male factor infertility were more often born SGA than men with all other causes of infertility, although this did not reach statistical significance.

More men in couples with infertility were born with non-optimal birth characteristics compared with the reference group consisting of all Swedish men of the same age; the difference was most pronounced for men in couples with male or combined factor infertility. Men with infertility diagnoses were excluded from the control group, but some of the men may have unknown poor semen parameters because they have not yet tested their fertility. The proportion of non-optimal birth characteristics in the whole reference group is therefore also reported. Because of the large size of the reference group, this number of men with 'unknown male factor infertility' probably does not affect the results. Hence, our results suggest an association between non-optimal birth characteristics and male factor infertility.

One possible explanation of this association is that cryptorchidism, more common among children born with non-optimal birth characteristics, relates to lower sperm concentration and motility (*Depue, 1984*; *Main et al., 2006*; *Hart et al., 2015*; *Adomaitis et al., 2016*; *Olesen et al., 2017*). We do not, however, have data on how many men in this study were born with cryptorchidism. Males born SGA also have a higher risk of developing metabolic syndrome and obesity later in life (*Barker et al., 1993*; *Barker 2007*; *Labayen et al., 2008*; *Simmons, 2008*; *Ross and Desai, 2013*). The metabolic syndrome was, in a study of primary infertile men, associated with a lower general health status and lower levels of testosterone, anti-Müllerian hormone, sex hormone-binding globulin and inhibin-B, without evidently affecting sperm parameters (*Ventimiglia et al., 2016*). Studies focusing on inflammation, insulin resistance and

TABLE 2 BIRTH CHARACTERISTICS IN MEN BY DIAGNOSED FACTOR OF INFERTILITY AND AMONG MEN IN THE REFERENCE GROUP AND CONTROL GROUP (ABSOLUTE NUMBER AND PER CENT).

	Index men												Reference group		Control group			
	Diagnosed factor of infertility																	
	Unexplained		Female		Male		Combined		Total		Male + Combined		MBR		MBR, 2 controls		Male versus reference	Male versus control
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*-value[a]	*P*-value[b]
	215	24.1	297	33.3	182	20.4	198	22.2	892	100.0	380	42.6	*n* = 538839	*n* = 1784				
PTB (< week 37)																0.890	0.962	
No	204	94.9	279	93.9	173	95.1	184	93.4	840	94.3	357	94.2	510941	94.8	1698	95.2		
Yes	11	5.1	18	6.1	9	4.9	13	6.6	51	5.7	22	5.8	27898	5.2	86	4.8		
LBW (<2500 g)																0.732	0.424	
No	208	96.7	288	97.0	175	96.2	187	94.4	858	96.2	362	95.3	520415	96.6	1734	97.2		
Yes	7	3.3	9	3.0	7	3.8	11	5.6	34	3.8	18	4.7	18424	3.4	50	2.8		
SGA																0.059	0.087	
No	207	97.6	277	95.8	163	93.1	185	95.4	832	95.6	348	91.8	517051	96.0	1711	95.9		
Yes	5	2.4	12	4.2	12	6.9	9	4.6	38	4.4	21	8.2	21788	4.0	73	4.1		
LGA																		
No	207	97.6	280	96.9	170	97.1	187	96.4	844	97.0	357	96.7	523915	97.2	1751	98.2	0.886	0.712
Yes	5	2.4	9	3.1	5	2.9	7	3.6	26	3.0	12	3.3	14924	2.8	33	1.8		
Non-optimal birth																		
characteristics																		
No	194	90.2	259	87.2	155	85.2	171	86.4	779	87.3	326	85.8	477461	88.6	1632	91.5	<0.001	0.010
Yes	21	9.8	38	12.8	27	14.8	27	13.6	113	12.7	54	14.2	61378	11.4	152	8.5		

[a] *P*-value refers to comparison of men with male factor infertility and men in the Medical Birth Register (MBR). Significance level $P < 0.05$; Bonferroni adjusted *P*-values from Pearson's chi-squared test.

[b] *P*-value refers to comparison of men with male factor infertility and two male controls from the MBR, matched on year of birth. Significance level $P < 0.05$; Bonferroni adjusted *P*-values from Pearson's chi-squared test.

LBW, low birth weight; LGA, large for gestational age; PTB, preterm birth; SGA, small for gestational age.

TABLE 3 LOGISTIC REGRESSION FOR NON-OPTIMAL BIRTH CHARACTERISTICS AMONG DIFFERENT DIAGNOSED FACTORS OF INFERTILITY AMONG MEN

	Male versus unexplained		Combined versus unexplained		Male + combined versus unexplained		Male versus female		Male + combined versus female	
	Crude OR (95% CI)	OR (95% CI)[a]	Crude OR (95% CI)	OR (95% CI)[a]	Crude OR (95% CI)	OR (95% CI)[a]	Crude OR (95% CI)	OR (95% CI)[a]	Crude OR (95% CI)	OR (95% CI)[a]
PTB										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.96 (0.39 to 2.38)	0.66 (0.23 to 1.86)	1.31 (0.57 to 3.00)	1.36 (0.58 to 3.20)	1.43 (0.65 to 3.12)	1.25 (0.54 to 2.90)	0.81 (0.35 to 1.84)	0.53 (0.20 to 1.38)	1.07 (0.56 to 2.01)	0.88 (0.45-1.70)
LBW										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	*Reference*
Yes	1.19 (0.41 to 3.45)	1.08 (0.33 to 3.53)	1.75 (0.66 to 4.60)	1.62 (0.56 to 4.68)	2.18 (0.81 to 5.86)	2.11 (0.70 to 6.42)	1.28 (0.47 to 3.50)	1.06 (0.36 to 3.14)	1.94 (0.85 to 4.45)	1.37 (0.60-3.15)
SGA										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	*Reference*
Yes	3.05 (1.05 to 8.23)	4.84 (1.32 to 17.80)	2.01 (0.66 to 6.12)	2.15 (0.53 to 8.78)	2.34 (0.87 to 6.27)	2.98 (0.86 to 10.39)	1.70 (0.75 to 3.87)	1.84 (0.76 to 4.47)	1.47 (0.70 to 3.09)	1.24 (0.56-2.77)
Non-optimal birth characteristic										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	*Reference*
Yes	1.61 (0.88 to 2.96)	1.60 (0.83 to 3.09)	1.46 (0.80 to 2.67)	1.37 (0.71 to 2.64)	1.60 (0.92 to 2.76)	1.54 (0.84 to 2.80)	1.19 (0.70 to 2.02)	1.07 (0.61 to 1.89)	1.13 (0.72 to 1.76)	1.00 (0.62-1.60)

[a] Adjusted for body mass index and smoking.

LBW, low birth weight; PTB, preterm birth; SGA, small for gestational age.

dyslipidaemia, all known contributing factors for the metabolic syndrome, have shown elevated oxidative stress leading to increased sperm DNA damage and negative effects on sperm development (*Morrison and Brannigan, 2015*).

Obesity affects male fertility, for which alterations in sperm parameters, including DNA fragmentation, epigenetic changes and down-regulation of the androgenic axis have been shown (*Craig et al., 2017*). Obese men have a reduced rate of live birth per cycle of ART (*Campbell et al., 2015*). More than one-half (52%) of the men in the present study were either overweight or obese. This, however, was a trend in the entire clinical sample studied, not only in those with a male cause of infertility. In an annual survey conducted by the Public Health Agency in Sweden, men aged between 16 and 84 years reported BMI and other health data. Between 2005 and 2010, the self-reported prevalence of BMI over 24.9 was between 52 and 58% in the southeast of Sweden, the region of residence of most patients in the present study (*Public Health Agency of Sweden, 2015*). Hence, the proportion of obese men is roughly the same in the patient group as it is in the population. In the subgroup of men born SGA, 51.5% were overweight or obese; i.e. men born SGA were not more often overweight or obese than men in the population. The analysis comparing the likelihood of being born with non-optimal birth characteristics between men with different infertility factors was adjusted for BMI (and smoking). The results after adjustment are similar and the association found in our study between male infertility and SGA can, therefore, not be explained by obesity *per se*. The unadjusted OR was 3.05 (95% CI 1.05 to 8.83), indicating that BMI in adulthood is related to intrauterine growth, which was discussed previously.

A previous study on a Nordic population, for whom snuff use is common, showed that men using snuff had lower total sperm count, sperm concentration and motility (*Parn et al., 2015*). This is also consistent with the known fact that tobacco smokers have lower sperm parameters (*Borges et al., 2018*). The association between snuff use and sperm parameters in the present study is actually the opposite. Men with male and combined factor infertility more seldom used snuff than men with normal sperm samples. One possible interpretation is that men stop using snuff after being informed about their affected sperm sample, but sperm parameters have still not improved (or they have improved, but are still abnormal). The matter would be clarified if data on previous snuff use were available, but this information could not be retrieved from the questionnaires.

The outcomes of the intervention with IVF/ICSI in the present study did not differ between men born with optimal versus non-optimal birth characteristics, nor between men with different factors of infertility. This positive result for both groups is an indication that ART is an equally effective method for men born SGA, as it is for men with normal birth characteristics.

In the present study, no adjustments were made for female factors such as age, number of oocytes retrieved and dose of gonadotrophins. The median birth year of the female partners was 1976 (between 29 and 34 years of age at the first treatment), and 71.5% had a BMI less than 25 kg/m^2 (*Vikstrom et al., 2014*). Women with high ovarian reserve, e.g. women with anovulation because of polycystic ovarian syndrome, as well as low ovarian reserve, were included in the female factor group, and, therefore, the number of oocytes retrieved and the dose of gonadotrophins used may have varied between the individuals. The median oocyte number and dose of gonadotropins are estimated

TABLE 4 TREATMENT OUTCOMES AND TREATMENT CHOSEN REPORTED BY DIAGNOSED FACTOR OF INFERTILITY

	Diagnosed factor of infertility																
	Unexplained (101)		Female (220)		Male (88)		Combined (133)		Total (542)		Male + Combined (221)		Male versus unexplained	Male versus female	Male versus combined	Male + combined versus unexplained	Male + combined versus female
	n	%	*n*	%	*n*	%	*n*	%	*n*	%		%	*P*-value[a]	*P*-value[a]	*P*-value[a]	*P*-value[a]	*P*-value[a]
Pregnancy													0.448	1.000	0.080	1.000	1.000
No	61	60.4	123	55.9	43	48.9	80	60.2	307	56.6	123	55.7					
Yes	40	39.6	97	44.1	45	51.1	53	39.8	235	43.4	98	44.3					
Child													0.096	0.260	0.116	0.848	1.000
No	69	68.3	140	63.6	46	52.3	89	66.9	344	63.5	135	61.1					
Yes	32	31.7	80	36.4	42	47.7	44	33.1	198	36.5	86	38.9					
Type of first treatment[b]													<0.001	<0.001	0.112	<0.001	<0.001
IVF	65	64.4	125	56.8	24	27.3	60	45.1	274	50.6	84	38.0					
ICSI	13	12.9	52	23.6	51	58.0	58	43.6	174	32.1	109	49.3					
Other	23	22.8	43	19.5	13	14.8	15	11.3	94	17.3	28	12.7					
Type of treatment (all)[c]													<0.001	<0.001	0.700	<0.001	<0.001
IVF	73	72.3	134	60.9	30	34.1	62	46.6	299	55.2	92	41.6					
ICSI	19	18.8	62	28.2	55	62.5	68	51.1	204	37.6	123	55.7					
Other	9	8.9	24	10.9	3	3.4	3	2.3	39	7.2	6	2.7					

[a] Significance level $P < 0.05$. Bonferroni adjusted *P*-values from Pearson's chi-squared test.

[b] The first treatment carried out for each man.

[c] Every treatment carried out for each man included. ICSI was selected if ICSI was carried out once or more than once; IVF was selected if IVF was carried out once or more than once and ICSI was not carried out; and other was chosen if IVF and ICSI were never carried out.

ICSI, intracytoplasmic sperm injection.

to be similar between groups with different infertility factors.

Almost one-third of all couples (31%) going through an infertility evaluation did not continue with any treatment at our unit after being diagnosed. The cause is unknown but we can speculate about reasons such as spontaneously conceived pregnancy, decision to postpone treatment, couple separation or change of IVF clinic.

A limitation of this study is the difficulty in diagnosing infertility factors. Male factor infertility in its most absolute form (azoospermia) might seem easy to diagnose; however, as sperm parameters differ between semen samples delivered at different occasions, at least two samples must be abnormal before a male factor can be established. In clinical practice, no further semen samples are collected or analysed if the first sample is normal according to WHO criteria (*Cooper et al., 2010*). If the examination of the female partner does not find any abnormalities, then the couple will be diagnosed with unexplained infertility. When, and if, a couple with unexplained infertility continues with ART treatment, a semen sample is collected for each treatment cycle and might be abnormal. In the present study, men with two or more abnormal semen samples are diagnosed with male factor infertility even if the first sample was normal. Men diagnosed with unexplained infertility based on one normal semen sample analysis during the investigation phase remain in this infertility category even if their semen sample in the first ART cycle is abnormal. The infertility factor may be more or less correctly diagnosed depending on how many semen samples the man provides.

One of the strengths of the study is the use of the validated national register MBR when collecting data regarding birth weight and gestational age. The risk of recall bias that might be present when using self-reported data is thereby eliminated. Given the study design, this is also a rather large population in a clinical setting. Another strength of the study is that the patients are from rural and urban areas and as the initial treatment cycles are publicly funded, patients from different socioeconomic groups have the possibility to start ART cycles at RMC. No information on sociodemographic factors could be retrieved in the reference group (and thus the control group). This limited the methods of analyses to purely descriptive analyses, i.e. comparisons of the distribution of non-optimal birth characteristics between the different groups.

The hypothesis that men with LBW, SGA and PTB have a higher risk for male factor infertility in adulthood is supported by some of the data in this study. Men with male or combined factor infertility have a higher probability of being born SGA, with LBW, or both, than men with unexplained or female factor (OR >1 in all groups) (TABLE 4). The 95% confidence intervals include 1 in most of the comparisons, indicating a lack of power, but the results still suggest an increased risk for male infertility among men born with non-optimal birth characteristics. A proportion of 4.2% of men in couples with female factor infertility were born SGA, which is rather similar to the prevalence of SGA in the reference material (4.0%). In the group of men with male factor, 6.9% were born SGA. Again, the small total number of men with non-optimal birth characteristics in each infertility factor group probably explains why this difference between male and female factor infertility is not statistically significant.

The study shows that the intrauterine milieu may have clinical implications for fertility later in life, and the ongoing efforts worldwide to try and improve the health of pregnant women and minimizing risk factors such as tobacco use during pregnancy must continue.

In conclusion, men in couples with infertility, regardless of infertility factor, tend to be born more often with LBW, SGA or preterm compared with all Swedish men of the same age. The difference was more pronounced for men with male or combined factor infertility. Being SGA at birth was almost five times more likely for men with male factor infertility than for men with unexplained infertility.

ACKNOWLEDGEMENTS

This study was supported by ALF grants, The County Council of Östergötland.

REFERENCES

Adomaitis, R., Vincel, B., Eidukaite, A., Ostaneviciute, E., Kirka, R., Bilius, V., Malcius, D., Verkauskas, G., Hadziselimovic, F. **Consequences of bilateral cryptorchidism in adults.** Andrologia 2016; 48: 933–938

Barker, D.J. **The origins of the developmental origins theory.** J. Intern. Med. 2007; 261: 412–417

Barker, D.J., Hales, C.N., Fall, C.H., Osmond, C., Phipps, K., Clark, P.M. **Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth.** Diabetologia 1993; 36: 62–67

Barker, D.J.P. 1998 **Mothers.** Babies and Health in Later Life Churchill Livingstone Edinburgh Scotland

Boeri, L., Ventimiglia, E., Capogrosso, P., Ippolito, S., Pecoraro, A., Paciotti, M., Scano, R., Galdini, A., Valsecchi, L., Papaleo, E., Montorsi, F., Salonia, A. **Low Birth Weight Is Associated with a Decreased Overall Adult Health Status and Reproductive Capability - Results of a Cross-Sectional Study in Primary Infertile Patients.** PLoS One 2016; 11e0166728

Borges, E.Jr., Braga, D., Provenza, R.R., Figueira, R.C.S., Iaconelli, A.Jr., Setti, A.S. **Paternal lifestyle factors in relation to semen quality and in vitro reproductive outcomes.** Andrologia 2018: e13090

Campbell, J.M., Lane, M., Owens, J.A., Bakos, H.W. **Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis.** Reprod. Biomed. Online 2015; 31: 593–604

Cicognani, A., Alessandroni, R., Pasini, A., Pirazzoli, P., Cassio, A., Barbieri, E., Cacciari, E. **"Low birth weight for gestational age and subsequent male gonadal function.** J. Pediatr. 2002; 141: 376–379

Cooper, T.G., Noonan, E., von Eckardstein, S., Auger, J., Baker, H.W., Behre, H.M., Haugen, T.B., Kruger, T., Wang, C., Mbizvo, M.T., Vogelsong, K.M. **World Health Organization reference values for human semen characteristics.** Hum. Reprod. Update 2010; 16: 231–245

Craig, J.R., Jenkins, T.G., Carrell, D.T., Hotaling, J.M. **Obesity, male infertility, and the sperm epigenome.** Fertil. Steril. 2017; 107: 848–859

deKeyser, N., Josefsson, A., Bladh, M., Carstensen, J., Finnstrom, O., Sydsjo, G. **"Premature birth and low birthweight are associated with a lower rate of reproduction in adulthood: a Swedish population-based registry study.** Hum. Reprod. 2012; 27: 1170–1178

Depue, R. **Maternal and gestational factors affecting the risk of cryptorchidism and inguinal hernia.** Int. J. Epidemiol. 1984; 13: 311–318

Faure, C., Dupont, C., Chavatte-Palmer, P., Gautier, B., Levy, R., Group, A.C. **Are semen parameters related to birth weight?** Fertil. Steril. 2015; 103: 6–10

Francois, I., de Zegher, F., Spiessens, C., D'Hooghe, T., Vanderschueren, D. **Low birth weight and subsequent male subfertility.** Pediatr. Res. 1997; 42: 899–901

Hart, R.J., Doherty, D.A., McLachlan, R.I., Walls, M.L., Keelan, J.A., Dickinson, J.E., Skakkebaek, N.E., Norman, R.J., Handelsman, D.J.

Testicular function in a birth cohort of young men. Hum. Reprod. 2015; 30: 2713–2724

Hodgson and Coe. 2005 **Perinatal programming: Early Life Determinants of Adult Health and Disease.** Taylor & Francis

Keller, M., Felderhoff-Mueser, U., Lagercrantz, H., Dammann, O., Marlow, N., Huppi, P., Buonocore, G., Poets, C., Simbruner, G., Guimaraes, H., Mader, S., Merialdi, M., Saugstad, O.D. **Policy benchmarking report on neonatal health and social policies in 13 European countries.** Acta Paediatr. 2010; 99: 1624–1629

Labayen, I., Moreno, L.A., Ruiz, J.R., Gonzalez-Gross, M., Warnberg, J., Breidenassel, C., Ortega, F.B., Marcos, A., Bueno, M., Avena Study, G. **Small birth weight and later body composition and fat distribution in adolescents: the Avena study.** Obesity (Silver Spring) 2008; 16: 1680–1686

Liffner, S., Hammar, M., Bladh, M., Nedstrand, E., Martinez, H.R., Sydsjo, G. **Men becoming fathers by intracytoplasmic sperm injection were more often born small for gestational age.** Asian J. Androl. 2017; 19: 103–106

Main, K.M., Jensen, R.B., Asklund, C., Hoi-Hansen, C.E., Skakkebaek, N.E. **Low birth weight and male reproductive function.** Horm. Res. 2006; 65: 116–122

Marsal, K, P.P.-H., Larsen, T, Lilja, H, Selbing, A, Sultan, B **Intrautering growth curves based on ultrasonically estimated foetal weights.** Acta Paediatr. 1996; 85: 843–848

McMillen, I.C., Robinson, J.S. **Developmental origins of the metabolic syndrome: prediction, plasticity, and programming.** Physiol. Rev. 2005; 85: 571–633

Morrison, C.D., Brannigan, R.E. **Metabolic syndrome and infertility in men.** Best Pract. Res. Clin. Obstet. Gynaecol. 2015; 29: 507–515

National Board of Health and Welfare, C. f. E. (2003). "The Swedish Medical Birth Register - A summary of Content and Quality."

National Board of Health and Welfare, C. f. E. (2009). "Pregnancies, Deliveries and Newborn Infants; The Swedish Medical Birth Register 1973-2007; Assited Reproduction, treatment 1991-2006."

Olesen, I.A., Andersson, A.M., Aksglaede, L., Skakkebaek, N.E., Rajpert-de Meyts, E., Joergensen, N., Juul, A. **Clinical, genetic, biochemical, and testicular biopsy findings among 1,213 men evaluated for infertility.** Fertil. Steril. 2017; 107: 74–82

Ozturk, O., Armstrong, K., Bhattacharya, S., Templeton, A. **Fetal antecedents of male factor sub-fertility: how important is birthweight?** Hum. Reprod. 2001; 16: 2238–2241

Parn, T., Grau Ruiz, R., Kunovac Kallak, T., Ruiz, J.R., Davey, E., Hreinsson, J., Wanggren, K., Salumets, A., Sjostrom, M., Stavreus-Evers, A., Ortega, F.B., Altmae, S. **Physical activity, fatness, educational level and snuff consumption as determinants of semen quality: findings of the ActiART study.** Reprod. Biomed. Online 2015; 31: 108–119

Public Health Agency of Sweden. (2015). "Vikt, BMI (självrapporterat) efter region, kön och år." Retrieved September, 28, 2017, from http://fohm-app.folkhalsomyndigheten.se/Folkhalsodata/pxweb/sv/B_HLV/B_HLV__aLevvanor__aahLevvanorvikt/zHLV_Viktobmi_regionalt.px/table/tableViewLayout1/?rxid=b90c9ce3-2ce5-45bc-9321-c2880ed5550e.

Ramlau-Hansen, C.H., Hansen, M., Jensen, C.R., Olsen, J., Bonde, J.P., Thulstrup, A.M. **"Semen quality and reproductive hormones according to birthweight and body mass index in childhood and adult life: two decades of follow-up.** Fertil. Steril. 2010; 94: 610–618

Ross, M.G., Desai, M. **Developmental programming of offspring obesity, adipogenesis, and appetite.** Clin. Obstet. Gynecol. 2013; 56: 529–536

Simmons, R. **Perinatal programming of obesity.** Semin Perinatol. 2008; 32: 371–374

Ventimiglia, E., Capogrosso, P., Colicchia, M., Boeri, L., Serino, A., Castagna, G., Clementi, M.C., La Croce, G., Regina, C., Bianchi, M., Mirone, V., Damiano, R., Montorsi, F., Salonia, A. **Metabolic syndrome in white European men presenting for primary couple's infertility: investigation of the clinical and reproductive burden.** Andrology 2016; 4: 944–951

Vikstrom, J., Hammar, M., Josefsson, A., Bladh, M., Sydsjo, G. **Birth characteristics in a clinical sample of women seeking infertility treatment: a case-control study.** BMJ Open 2014; 4e004197

Whitcomb, B.W., Bloom, M.S., Kim, S., Chen, Z., Buck Louis, G.M. **Male birthweight, semen quality and birth outcomes.** Hum. Reprod. 2017; 32: 505–513

WHO, W. H. O. (2000). Obesity: preventing and managing the global epidemic: report of a WHO consultation. WHO technical report series. Geneva, Switzerland.

Zegers-Hochschild, F.G.D., Adamson, J., de Mouzon, O., Ishihara, R., Mansour, K., Nygren, E., Sullivan, S., Vanderpoel, T. **International Committee for Monitoring Assisted Reproductive and O. World Health. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009.** Fertil. Steril. 2009; 92: 1520–1524

Received 22 April 2020; accepted 27 April 2020.