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## ORIGINAL ARTICLE

Male Fertility

# Men becoming fathers by intracytoplasmic sperm injection were more often born small for gestational age

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Being born with nonoptimal birth characteristics decreases the chance of becoming a father. Urogenital malformations as well as metabolic syndrome are more common in men born small for gestational age (SGA) and could be contributing factors to the reduced fertility rate seen in these men. It could imply that men becoming fathers by assisted reproductive technology (ART) more often are born with low birth weight (LBW), preterm, and/or SGA than men conceiving without treatment and also that men where intracytoplasmic sperm injection (ICSI) had to be performed more often are born with nonoptimal birth characteristics than men where conventional *in vitro* fertilization (IVF) successfully could be used. In this retrospective, case–control study using Swedish national registers, we compared the birth characteristics of 1206 men who have become fathers by ART with a control group consisting of age-matched men who became fathers without treatment. The differences in birth characteristics between men becoming fathers by IVF and ICSI were also assessed. For men becoming fathers by ART, OR of being born with LBW was 1.66 (95% CI = 1.17–2.36) compared with fathers who conceived without treatment. OR of being born prematurely was 1.32 (95% CI = 1.00–1.77). Men becoming fathers via ICSI had a doubled increased likelihood of being born SGA compared with men who became fathers via IVF (OR = 2.12; 95% CI = 1.17–3.83). In conclusion, we have found that men becoming fathers by ICSI treatments had more often been born SGA than men becoming fathers by conventional IVF.

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## INTRODUCTION

Men with nonoptimal birth characteristics have a lower reproductive rate than men with normal birth characteristics.<sup>1</sup> Being born preterm or with LBW decreases the chance of becoming a father. Males aged 31–33 years born SGA had a 10% lower rate of reproduction compared with men with normal birth characteristics whereas the reproductive rate of younger men could not be shown to differ from controls.<sup>1</sup> SGA is often a token for impaired fetal growth not related to prematurity. Associations between LBW and unexplained male subfertility, high peripheral FSH levels, low levels of inhibin-B, and small testicular volume in adolescence have been registered.<sup>2,3</sup> However, a direct relationship between LBW and sperm quality remains to be established.<sup>4,5</sup> Ozturk *et al.*<sup>4</sup> could not find any differences in birth weight between men with abnormal sperm parameters and men with normal sperm parameters. All men in that study were patients in an infertility clinic indicating that the controls had a lower reproductive rate than average, and this could be a reason for the lack of difference between the groups. In the study of Ramlau-Hansen *et al.*,<sup>5</sup> all men had been born after gestational week 36 ruling out prematurity. LBW was defined in their study as a birth weight between 1710 and 3250 g.

Using our criterion for LBW – birth weight <2500 g – only 8 of 347 participants in their study were LBW.

Previous research has shown an association between restricted intrauterine growth and the development of the metabolic syndrome later in life.<sup>6,7</sup> Obesity, which is a part of the metabolic syndrome, seems to impair sperm quality whereas insulin resistance has been shown not to affect sperm quality.<sup>8–10</sup>

When treating infertility caused by male factors, the use of conventional IVF is often not sufficient. The introduction of ICSI in 1992 made it possible to treat infertility caused by severe oligozoospermia or asthenozoospermia since only one viable and presumably fertile spermatozoon is needed for each retrieved oocyte.<sup>11</sup> ICSI was rapidly integrated into the routine clinical repertoire and was already by 2004 the most frequently (58.9%) used method for assisted fertilization worldwide.<sup>12</sup> The proportion of male-related infertility in couples treated with ART was 37%–47% and it is obvious that ICSI was used on the basis of indications other than oligozoospermia.<sup>12</sup> ICSI is less frequently used in the Nordic countries than worldwide; in 2004, ICSI was used in 49.1% of Swedish ART treatments.<sup>12</sup> In Sweden, ICSI is often used when fertilization failure occurred with conventional

IVF and it was almost always used in the past when handling donated gametes to minimize the risk of fertilization failure. At present, the standard treatment is IVF even in donation cycles.

As reproductive rate is lower in men born with nonoptimal birth characteristics, we hypothesized that they are overrepresented in couples needing treatment with ART to be able to conceive. We also hypothesized that ICSI would have to be used more often in relation to conventional IVF in couples where the male partner had been born with nonoptimal birth characteristics than in couples where the man was born with normal birth weight and at term. This hypothesis is based on our assumption that ICSI is used either because of an evident male factor or due to a preceding unsuccessful fertilization with conventional IVF.

Thus, this retrospective, case-control study using national registers aimed at determining whether ART-need was higher for men born with nonoptimal birth characteristics to be able to conceive and whether there was a difference between the need to apply conventional IVF or ICSI in relation to various birth characteristics (birth weight, prematurity, and size for gestational age) in men who became fathers by ART.

## MATERIALS AND METHODS

### Register data

Since 1982, information on children conceived by ART in Sweden has been reported to the National Board of Health and Welfare by all centers performing ART. In the mid-1990s, a register, approved by the Swedish Data Inspection Board, of all ART treatments resulting in the delivery of a child was created. The initial intention of this register was to collect data to enable studies of possible health risks for children conceived after ART and information regarding treatment cycles not resulting in childbirth was not registered. The database contains information on all births after ART performed between 1982 and 2006.

Since 1973, information regarding 97%–99% of all births in Sweden has been reported to the Swedish Medical Birth register (MBR).<sup>13</sup> The register includes information regarding complications during pregnancy, delivery, and the neonatal period as well as maternal reproductive history. Data concerning birth weight and gestational age at birth of all men in this study were retrieved from this register.

Nonoptimal birth characteristics were defined as low birth weight (LBW) <2500 g either due to prematurity, intrauterine growth retardation, or both, preterm birth <37 weeks, small for gestational age (SGA) <-2s.d. of the mean weight for the gestational length, and large for gestational age (LGA) >+2s.d. of the mean weight for the gestational length.<sup>14</sup>

### Study population

All 6060 births after successful ART, where the mother was born between January 1, 1973, and December 31, 1983, were registered between December 11, 1998, and December 31, 2006. By use of the Multi-Generation Register, we have been able to identify the fathers of 4023 of these children.<sup>15</sup> Men born before 1973 or outside of Sweden were excluded in the study since their birth characteristics were not registered in MBR; thus, leaving 1206 unique men who have become fathers by ART and whose birth weight was known. We also know in which gestational week 1195 of these men were born. A control group was constructed which consisted of four age-matched men per index man randomly selected from the Multi-Generation Register. The men in the control group had become fathers without ART at the same age as each man in the index group.

The register of all ART treatments resulting in delivery was used to determine if nonoptimal birth characteristics of the father were more common in ART where ICSI or conventional IVF was performed.

### Statistics

Data are presented as absolute numbers and percentages. Pearson's Chi-square test was used to assess the bivariate differences between birth characteristics in the groups (index and control) as well as type of treatment and birth characteristics among men who had become fathers through IVF or ICSI.

All analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A  $P < 0.05$  was considered statistically significant.

### Ethics

The study was approved by The Regional Ethical Review Board in Linköping, Dnr M233-08, December 10, 2008, and Dnr 2010/403-31, January 26, 2011.

## RESULTS

The birth characteristics of the index men and controls are shown in **Table 1**. A higher percentage of men were born with LBW (4.1%) among those fathering via ART, compared to controls (2.5%),  $P = 0.048$ . In the index group, 5.8% of the men were born preterm compared with 4.4% of the controls ( $P = 0.051$ ). This is equivalent to an increased likelihood for men fathering via ART to be born with LBW and preterm compared with controls (OR = 1.66; 95% CI = 1.17–2.36 and OR = 1.32; 95% CI = 1.00–1.77 respectively). There was no difference in the use of ART among men born small, appropriate, or large for gestational age ( $P = 0.85$ ) compared with controls. To further elucidate the relationship between size for gestational age and ways of conceiving, the ART group was separated into those treated with ICSI and those who underwent conventional IVF. In these analyses, it was found that men treated with ICSI had an increased likelihood of being SGA compared to controls (OR = 1.54; 95% CI = 1.04–2.30) while there was no difference between those treated with conventional IVF and controls (OR = 0.73; 95% CI = 0.44–1.20).

ICSI was used as ART-method for 539 of the 1195 men (45%) with known weight and gestational age at birth (**Table 2**). Men treated

**Table 1: Birth characteristics of fathers**

	ART fathers		Fathers born 1973–1983*		P	OR (95% CI)
	n	Percentage	n	Percentage		
Birth weight					0.048	
Low	49	4.1	98	2.5		1.66 (1.17–2.36)
Normal	1157	95.9	3848	97.5		Reference
Prematurity					0.051	
Preterm	69	5.8	174	4.4		1.32 (1.00–1.77)
Term	1126	94.2	3772	95.6		Reference
Size for gestational age					0.85	
SGA	49	4.1	148	3.8	0.58†	1.10 (0.79–1.52)
AGA	1115	93.3	3692	93.6		Reference
LGA	31	2.6	106	2.7	0.88††	0.97 (0.64–1.45)
Nonoptimal birth characteristic					0.42	
No	1088	90.2	3542	89.8		Reference
Yes	118	9.8	404	10.2		0.95 (0.77–1.18)

\*Among those who had become parents until December 31, 2006; †Comparison between SGA and AGA; ††Comparison between LGA and AGA. SGA: small for gestational age; AGA: average for gestational age; LGA: large for gestational age; ART: assisted reproductive technology; OR: odds ratio; CI: confidence interval

**Table 2: Birth characteristics of ART fathers by type of treatment**

	ICSI		IVF		P*	OR (95%CI)
	n	Percentage	n	Percentage		
Birth weight					0.98	
Low	22	4.0	27	4.1		0.99 (0.56–1.76)
Normal	522	96.0	635	95.9		Reference
Prematurity					0.47	
Preterm	34	6.3	35	5.3		1.20 (0.74–1.94)
Term	505	93.7	621	94.7		Reference
Size for gestational age					0.004	
SGA	31	5.8	18	2.7	0.010*	2.12 (1.17–3.83)
AGA	500	92.8	615	93.8		Reference
LGA	8	1.5	23	3.5	0.035**	0.43 (0.19–0.96)
Nonoptimal birth characteristic					0.26	
No	485	89.1	603	91.1		Reference
Yes	59	10.9	59	8.9		1.24 (0.85–1.82)

\*Pearson's Chi-square; \*Comparison between SGA and AGA; \*\*Comparison between LGA and AGA. SGA: small for gestational age; AGA: average for gestational age; LGA: large for gestational age; ICSI: intracytoplasmic sperm injection; IVF: *in vitro* fertilization; OR: odds ratio; CI: confidence interval; ART: assisted reproductive technology

with IVF were more often born appropriate for gestational age (AGA) or LGA than men treated with ICSI. This is manifested in a doubled increased likelihood of being born SGA for men treated with ICSI compared with conventional IVF (OR = 2.12; 95% CI = 1.17–3.83). Being born LBW did not affect the type of ART performed as 4.0% in the ICSI group and 4.1% in the IVF group were born LBW ( $P = 0.98$ ). Prematurity did not affect the use of ICSI since 6.3% of the men in the ICSI group were born preterm compared with 5.3% in the IVF group ( $P = 0.47$ ).

## DISCUSSION

Most men born in Sweden from 1973 to 1983 who became fathers after ART had been born at term with a normal birth weight, with only 5.8% of the total being born preterm and 4.1% born with LBW. This study shows a tendency of being born preterm and/or with LBW among those fathering via ART compared with controls. Since all data concerns men who became fathers by ART, it is possible that men born with nonoptimal birth characteristics were not able to conceive and, therefore, had more unsuccessful treatment cycles.

In any case, the results of our study suggest that it is not the actual birth weight nor prematurity that is important in future reproduction but SGA. SGA appears to be a better marker of poor nutritional status and restricted growth *in utero* than LBW. The etiology of being born SGA may differ, but maternal smoking during pregnancy is a known risk factor of SGA in the offspring and has also been associated with decreased sperm quality.<sup>16</sup> An association, based on self-reported data, has also been shown between maternal smoking during pregnancy and reduction of testicular capacity as well as earlier puberty, slightly reduced final height, and increased BMI in their sons.<sup>17</sup> Information from MBR regarding maternal smoking was only available for men born 1982 and 1983, which corresponds to 8 index men in our study. No conclusions could, therefore, be made regarding smoking exposure. Metabolic syndrome, including obesity, as well as urogenital malformations such as undescended testes and hypospadias, is more common in men with nonoptimal birth characteristics.<sup>18</sup> We do not, however, know the prevalence of urogenital malformations nor of the metabolic syndrome in our study population.

Men born SGA had consistently shown higher levels of estradiol, dihydrotestosterone, and inhibin-B than controls but had the same levels of testosterone, which might indicate a disturbed steroid synthesis with higher aromatase or 5 $\alpha$ -reductase activity.<sup>19</sup> The postnatal course of boys born SGA differs and there could be a difference in testicular capacity depending on received treatments, such as exogenous growth hormone, as well as differing growth curves during childhood and puberty. The postnatal treatment and growth of the men in this study are not known but could, of course, be factors affecting their reproductive capacity.

Among the men for whom ICSI had to be used, 5.8% had been born SGA compared with 2.7% of the men for whom conventional IVF could be used ( $P = 0.010$ ). Only 4.1% of the men conceiving by ART were born SGA, but 63% of them needed ICSI to become a father compared with 45% of the men born appropriate for gestational age (AGA) ( $P = 0.001$ ). Since ICSI is the method of choice in Sweden when the sperm quality is low or when previous treatment cycles have shown a low fertilization rate, we believe that one of the reasons why men born SGA have a 9% lower reproduction rate, as was shown by deKeyser *et al.*,<sup>1</sup> could be that the sperm quality is somehow impaired. Ramlau-Hansen *et al.*<sup>5</sup> could not find any differences in concentration, total amount, motility, or morphology of spermatozoa when comparing men born with low, normal, or high birth weight. However, their definition of LBW, 1710–3250g, was different from ours. Only 8 of the 347 participants in their study were born with LBW according to our criteria, which make comparisons of results difficult. Moreover, other sperm variables such as chromatin integrity and different protein expressions between fertilizing and nonfertilizing spermatozoa could very well lie behind these differences.<sup>20</sup> These are variables we (and others) do not routinely study, but they may affect the outcome of treatments even if sperm concentration, motility, and morphology are normal.

Returning to the matter of sperm quality as decision criterion for use of ICSI, it is relevant to point out that it is not known whether sperm quality parameters are impaired in men born SGA; this must be determined in future studies.

## Limitations

The mean age of becoming a father for the first time in Sweden was 28 years in 1982 and 31 years in 2006.<sup>21</sup> The oldest cohort (born 1973) turned 28 in 2001. In 2007, when the study closed, men born in 1983 were only 24 years old and most 24-year-old had not even started to try to conceive. This explains why the cohort of men becoming fathers by ART was relatively small.

It is a weakness that we do not know the specific reason in each case for using ICSI instead of conventional IVF. Our interpretation, however, is that use of ICSI could be regarded as a sign of lower sperm quality or low fertilization rate in previous treatment cycles, which is reasonable assuming that the ART centers followed the national guidelines. The proportion of ICSI cycles, 45%, is consistent with this assumption. The matter should be clarified in future studies.

## Strength of study

The strongest point in this study is that the birth weight and gestational age at birth are retrieved from MBR and are not self-reported; this largely diminishes selection biases.

In the register of ART treatments leading to childbirth, it is not possible to identify the cycles where donated gametes were used. If men born with nonoptimal birth characteristics have impaired sperm quality, there is a possibility that the proportion of men with azoospermia was greater in this group. Since only treatment cycles

resulting in childbirth were registered, it is probable that some of them were performed using sperm from donors. This may imply that the possibility of becoming a genetic father is even lower for men born with nonoptimal birth characteristics than the lower reproduction rate shown in the previous study by deKeyser *et al.*<sup>1</sup> The more frequent use of ICSI when treating men born SGA could be explained by impaired sperm quality but could also be caused, at least partly, by a higher incidence of ICSI treatments when frozen-thawed donated gametes had been used.

In this study of men with nonoptimal birth characteristics, it would have been interesting to have been able to compare all their ART treatment cycles (and not only the successful cycles resulting in childbirth), with the treatment cycles of men with normal birth characteristics. If a higher incidence of ICSI is caused by impaired sperm quality, it is plausible to consider that the probability to conceive with each treatment cycle is lower for men born with nonoptimal birth characteristics than for men with normal birth characteristics. Knowing that men born SGA have a lower reproduction rate and a greater need of ICSI to become fathers, it could be questioned if they also have an increased risk of unsuccessful ART cycles and miscarriages? Further studies are thus needed using data containing information on all treatment cycles and their results and also using a larger study population for which data are available on both the treatments and the parent's birth characteristics.

## CONCLUSION

We have found that men becoming fathers by ICSI treatments had more often been born SGA than men becoming fathers by conventional IVF.

## AUTHOR CONTRIBUTIONS

SL, MH, MB, EN, HRM, and GS all contributed to the design and interpretation of data and drafting of the manuscript. All authors have read and approved the final version of the manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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