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Low Birth Weight is Associated with Sperm DNA Fragmentation and Assisted Reproductive Technology Outcomes in Primary Infertile Men: Results of a Cross-Sectional Study

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Purpose: To assess the relationship between clinical and semen characteristics and assisted reproductive technology (ART) outcomes with different birth weight (BW) categories in a cohort of infertile men.

Materials and Methods: Data from 1,063 infertile men were analyzed. Patients with BW ≤2,500, 2,500–4,000, and ≥4,000 g were considered as having low BW (LBW), normal BW (NBW), and high BW (HBW), respectively. Testicular volume (TV) was assessed with a Prader orchidometer. Serum hormones were measured in all cases. Semen analyses were categorized based on 2021 World Health Organization reference criteria. Sperm DNA fragmentation (SDF) was tested in every patient and considered pathological for SDF >30%. ART outcomes were available for 282 (26.5%) patients. Descriptive statistics and logistic regression analyses detailed the association between semen parameters and clinical characteristics and the defined BW categories.

Results: Of all, LBW, NBW, and HBW categories were found in 79 (7.5%), 807 (76.0%), and 177 (16.5%) men, respectively. LBW men had smaller TV, presented higher follicle-stimulating hormone (FSH) but lower total testosterone levels compared to other groups (all $p<0.01$). Sperm progressive motility ($p=0.01$) and normal morphology ($p<0.01$) were lower and SDF values were higher (all $p<0.01$) in LBW compared to other groups. ART pregnancy outcomes were lower in LBW compared to both NBW and HBW categories (26.1% *vs.* 34.5% *vs.* 34.5%, $p=0.01$). At multivariable logistic regression analysis, LBW was associated with SDF >30% (odd ratio [OR] 3.7; $p<0.001$), after accounting for age, Charlson Comorbidity Index (CCI), FSH, and TV. Similarly, LBW (OR 2.2; $p<0.001$), SDF >30% (OR 2.9; $p<0.001$) and partner's age (OR 1.3; $p=0.001$) were associated with negative ART outcomes, after accounting for the same predictors.

Conclusions: LBW was associated with impaired clinical and semen characteristics in infertile men compared to both NBW and HBW. SDF and ART outcomes were significantly worse in the LBW group.

Keywords: Infant, low birth weight; Infertility; Reproductive techniques, assisted; Semen analysis

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INTRODUCTION

Infertility is a rising issue affecting approximately 15% of all couples of reproductive age [1,2]. In this context, epidemiological studies have shown that, after a comprehensive diagnostic work-up of both partners [1,3,4], a male factor can be found in 50% of the cases. Still, male infertility is idiopathic in approximately 30% of couples [5,6].

Various risk factors for male infertility have been found [6], such as recreational habits [7,8], medical conditions and genetic disorders [9-11], gonadotoxic treatments [1] and urological infections [12,13]. Moreover, recent evidence has shown that prenatal factors and in utero conditions might also impact future reproductive health [14]. The hypothesis of developmental origins of adult health and disease suggests an influence of the uterine environment on reproductive health in offspring through various processing, including parent's lifestyle, behavior and environmental exposure [15,16]. Nonetheless, the underline mechanisms for the association between male infertility and birth characteristics are not fully understood and are probably multifactorial and complex. Birth weight (BW) is an easily measurable factor that may reflect the influence of conditions that impact fetal growth and development and may predict long-term health outcomes [17,18].

Previous studies have investigated the association between BW, as a marker of fetal development, and male reproductive parameters with conflicting findings. A Swedish population-based registry study reported that men born with low BW (LBW) had a lower chance of becoming fathers than men born with normal birth characteristics [19]. Similarly, an Italian case-control study with 1,200 young adults showed that the prevalence of LBW was higher in infertile participants compared to the fertile counterpart (8.6% *vs.* 3.2%) [20]. Other studies, however, failed to show an association between birth characteristics and fertility outcomes [21]. The impact of BW on conventional semen parameters is even more conflicting. Indeed, some Authors have reported an association between LBW and sperm concentration, motility and morphology [20,22]; whereas others have found no relationship [21,23].

In this context, sperm DNA fragmentation (SDF) has increasingly gained clinical relevance in terms of reproductive outcomes both under natural and assisted reproductive technology (ART) conditions [24,25]. However, the impact of BW on SDF and ART outcomes has been poorly investigated.

Therefore, we aimed to cross-sectionally investigate the relationship between clinical and semen characteristics and ART outcomes with different categories of BW in a cohort of white-European men seeking first medical help for primary couple's infertility.

MATERIALS AND METHODS

1. Study cohort

We retrospectively analyzed data from a cohort of 1,343 white-European men consecutively assessed at a single academic center for primary couple's infertility between January 2015 and September 2021. According to World Health Organization (WHO) definition, couple's infertility was defined as not conceiving a pregnancy after at least 12 months of regular, unprotected intercourses regardless of whether or not a pregnancy ultimately occurs [26]. Patients were included if they were ≥18 and ≤55 years old and had male factor infertility (MFI) only, defined after a detailed diagnostic evaluation of all the female partners [27]. The female partner's evaluation included medical, reproductive and family history as well as a general and gynecological physical examination. Furthermore, the ovulatory status, ovarian reserve testing, the structure and patency of the female reproductive tract were requested in all cases [28].

Participants were investigated with a comprehensive medical history. The Charlson Comorbidity Index (CCI) was used to score health-significant comorbidities [29,30] and the body mass index (BMI) was calculated for each participant [31]. Testicular volume (TV) was recorded using Prader's orchidometer estimation [32]. Varicocele was clinically assessed in every man [1,3]. Smoking habit was investigated according to the pack-year history and then categorized into two groups, as follows: no smokers/former smokers, current smokers [7]. Infertility duration and partner's age were recorded in every participant [33]. BW was collected from the childhood health records of each individual. Patients with BW ≤2,500, 2,500–4,000, and ≥4,000 g were classified as having LBW, normal birth weight (NBW), and high birth weight (HBW), respectively [34,35].

Follicle-stimulating hormone (FSH), luteinizing hormone, total testosterone (tT), sex hormone-binding globulin, estradiol, inhibin B, and prolactin levels were measured for every individual. As per internal pro-

tocol, genetic testing and chromosomal analysis were performed in every man (karyotype analysis and tests for Y-chromosome microdeletions and cystic fibrosis mutations) [36].

Participants underwent at least two consecutive semen analyses [1,3,37]. As for clinical practice, we considered semen volume, sperm concentration, total sperm motility and normal morphology. Semen parameters were interpreted based on 2021 WHO reference criteria [38].

SDF, measured by Sperm Chromatin Structure Assay (SCSA), was requested for every participant and it was considered pathological for SDF >30% [3,39]. The same laboratory was used for the analysis of all parameters.

2. Exclusion criteria

Overall, we excluded 280 men because they missed one or more of the entry criteria (azoospermia [n=196; 14.5%]; genitourinary infections [n=13; 1.0%]; a history of vasectomy, undescended testicle, hypospadias or infertility treatment in the preceding year [n=31; 2.3%]; and, partial or incomplete data concerning one or more of the semen parameters considered [n=25; 1.8%] or without BW record [n=32; 2.3%]). A final sample of 1,063 infertile men was considered for the statistical analyses.

Pregnancy outcomes data, in terms of live birth rate, with ART were available for 282 (26.5%) patients. Of those, 14 (4.9%), 126 (44.6%), and 142 (50.5%) underwent intrauterine insemination, *in vitro* fertilization (IVF) and Intra Cytoplasmic Sperm Injection (ICSI), respectively.

3. Ethical approval

Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to share their own anonymous information for future studies. The study was approved by the San Raffaele Hospital. Approval number is provided (Prot.2014 etc).

4. Statistical methods

The Shapiro–Wilk test was used to test data distribution. Data are presented as medians (interquartile range) or frequencies (proportions). First, descriptive statistics was used to describe the whole cohort. Second, the Kruskal Wallis test and the Fisher exact test were used to investigate potential differences in clinical, laboratory, semen characteristics and ART outcome according to the established BW categories. Third, univariable and multivariable logistic regression analyses tested the association between predictors (age, CCI, FSH, TV, LBW, partner's age) and pathologic SDF and negative ART outcomes (as defined by the overall failure of any technique of ART). Statistical analyses were performed using SPSS version 26 (IBM Corp.). All tests were two-sided, and statistical significance level was determined at $p<0.05$.

RESULTS

Overall, LBW, NBW and HBW categories were found in 79 (7.5%), 807 (76.0%), and 177 (16.5%) men, respectively. Out of 1,063 participants, 545 (51.2%) had pathologic SDF and positive ART outcomes were found

Table 1. Characteristics and descriptive statistics of the whole cohort of patients (n=1,063)

	Value
Age (y)	
Median (IQR)	36 (33–40)
Range	18–55
BW (g)	
Median (IQR)	3,500 (3,150–3,850)
Range	1,100–6,300
BW	
LBW	79 (7.5)
NBW	807 (76.0)
HBW	177 (16.5)
BMI (kg/m^2)	
Median (IQR)	25.2 (23.4–27.3)
Range	18.1–45.0
CCI ≥1	106 (10.0)
Current smoking status	303 (28.5)
Testis volume (prader estimation)	
Median (IQR)	15 (12–20)
Range	2–25
Partner's age (y)	
Median (IQR)	34 (30–37)
Range	19–48
Duration of infertility (mo)	
Median (IQR)	18 (12–30)
Range	12–60
Varicocele	535 (50.3)
Subclinical	278 (51.9)
Grade I	197 (36.8)
Grade II	60 (11.3)

Table 1. Continued

	Value
FSH (mUI/mL)	
Median (IQR)	5.6 (3.4–11.0)
Range	0.1–83.7
LH (mUI/mL)	
Median (IQR)	4.2 (2.8–5.9)
Range	0.1–56.0
InhB (pg/mL)	
Median (IQR)	110.6 (50.5–168.6)
Range	6.0–790.0
tT (ng/mL)	
Median (IQR)	4.5 (3.4–5.7)
Range	0.9–51.8
E_2 (pg/mL)	
Median (IQR)	26.0 (23.7–38.4)
Range	2.2–139.0
SHBG (nmol/L)	
Median (IQR)	33 (25–42)
Range	6.0–90.0
Prolactin (ng/mL)	
Median (IQR)	8.6 (6.4–12.1)
Range	1.0–19.8
Semen volume (mL)	
Median (IQR)	3 (2–4)
Range	0.2–10
Sperm concentration ($\times 10^6$/mL)	
Median (IQR)	18.4 (5.0–47.0)
Range	0.5–305.9
Sperm concentration ≤16×10^6/mL	478 (44.9)
Progressive motility (%)	
Median (IQR)	23 (9–38)
Range	0–96
Progressive motility ≤30%	542 (50.9)
Normal morphology (%)	
Median (IQR)	2 (1–8)
Range	0–100
Normal morphology ≤4%	462 (43.4)
SDF (%)	
Median (IQR)	31.5 (18.8–49.3)
Range	0.5–100
SDF >30%	545 (51.2)
Assisted-pregnancy rate	116/282 (41.1)

Values are presented as number (%) otherwise indicated.
IQR: interquartile range, BW: birth weight, LBW: low BW, NBW: normal BW, HBW: high BW, BMI: body mass index, CCI: Charlson Comorbidity Index, FSH: follicle-stimulating hormone, LH: luteinizing hormone, InhB: inhibin B, tT: total testosterone, E_2: estradiol, SHBG: sex hormone-binding globulin, SDF: sperm DNA fragmentation.

in 116/282 (41.1%) couples (Table 1).

HBW men had higher BMI compared to those in both other groups (all p<0.001) (Table 2). A higher rate of CCI ≥1 was found in LBW men compared to both NBW and HBW (17.7% *vs.* 8.9% *vs.* 11.2%, p<0.01). LBW men had smaller TV than those in NBW and HBW groups, respectively (all p<0.001). Likewise, LBW patients presented higher FSH (p=0.01) and lower tT levels (p=0.01) as compared with men in the other groups (Table 2).

In terms of semen parameters, sperm progressive motility (p<0.01) and normal sperm morphology (p=0.03) were lower in LBW compared to the other groups (Table 3). Conversely, SDF values were higher (all p<0.01) in LBW and a higher rate of SDF >30% was found in LBW men (69.6%) compared to NBW (51.1%) and HBW (43.5%) (all p<0.01) (Table 3). Assisted pregnancy rate was lower in LBW compared to both NBW and HBW categories (26.1% *vs.* 34.5% *vs.* 34.5%, p=0.01).

Table 4 reports logistic regression analyses testing the association between clinical predictors and pathological SDF and negative ART outcomes. At multivariable logistic regression analysis, LBW (odd ratio [OR], 3.72; 95% confidence interval [CI] 1.91–7.49; p<0.001) and FSH values (OR, 1.85; 95% CI, 1.11–5.34; p<0.001) were associated with SDF >30%, after accounting for age, CCI, and TV. Likewise, age (OR, 1.20; 95% CI, 1.08–4.02; p=0.02), LBW (OR, 2.29; 95% CI, 1.13–8.84; p<0.001), SDF >30% (OR, 2.99; 95% CI, 2.10–10.19; p<0.001) and partner's age (OR, 1.34; 95% CI, 1.12–5.02; p=0.001) were found to be independently associated with negative ART outcomes, after accounting for CCI, FSH, and TV.

DISCUSSION

Over the last decades emerging data has shown that in utero conditions might affect offsprings' reproductive potential. In particular LBW, which is commonly used as a surrogate for impaired fetal growth and development, has been recognized to affect individual long-term somatic health as well as the gonadal and reproductive function [19,21]. Previous studies have explored the association between LBW and conventional semen parameters, but its impact on SDF and ART outcomes is currently poorly investigated. In this cross-sectional, real-life study we showed that men with LBW had lower values of sperm progressive motility and normal morphology than those in the NBW and

Table 2. Clinical characteristics and hormonal profile of infertile patients according to birth weight

	LBW	NBW	HBW	p-value[a]
No. of patients (n=1,063)	79 (7.5)	807 (76.0)	177 (16.5)	
Age (y)				0.6
Median (IQR)	36 (34–41)	36 (35–40)	36 (34–41)	
Range	22–55	18–54	20–55	
BMI (kg/m^2)				<0.001
Median (IQR)	24.4 (22.1–26.7)	25.2 (23.7–27.3)	26.1 (23.2–28.1)[b]	
Range	18.8–40.0	19.1–45.0	18.1–41.2	
CCI ≥1	14 (17.7)	72 (8.9)[b]	20 (11.2)[b]	<0.01
Current smoking status	23 (29.1)	227 (28.1)	53 (29.9)	0.2
Testis volume (prader estimation)				<0.001
Median (IQR)	15 (11–20)	18 (12–20)[b]	20 (13–25)[b]	
Range	3–25	2–25	7–25	
Partner's age (y)				0.5
Median (IQR)	34 (31–40)	34 (30–37)	34 (30–38)	
Range	21–48	19–48	20–47	
Duration of infertility (mo)				0.6
Median (IQR)	18 (12–29)	18 (12–29)	18 (12–30)	
Range	12–55	12–60	12–60	
Varicocele (n=535)	39 (49.4)	406 (50.3)	90 (50.8)	0.7
FSH (mUI/mL)				0.01
Median (IQR)	8.5 (3.3–14.4)	5.4 (3.5–11.0)[b]	5.7 (3.3–9.2)[b]	
Range	0.1–57.0	0.7–83.7	0.1–45.1	
LH (mUI/mL)				0.5
Median (IQR)	4.3 (2.8–6.3)	4.1 (2.9–6.0)	4.2 (3.0–5.2)	
Range	0.3–26.0	0.1–56.0	0.1–19.2	
InhB (pg/mL)				0.06
Median (IQR)	95.2 (43.3–155.8)	109.3 (48.8–170.1)	110.6 (50.7–155.4)	
Range	6.0–244.7	6.8–790.0	6.5–291.3	
tT (ng/mL)				0.01
Median (IQR)	4.1 (3.3–5.7)	4.8 (3.5–5.8)[b]	4.9 (3.2–5.6)[b]	
Range	1.8–10.7	0.9–51.8	1.2–9.9	
E_2 (pg/mL)				0.01
Median (IQR)	24.0 (21.1–32.5)	27.4 (24.5–39.2)[b]	24.5 (19.8–34.4)	
Range	5.0–94.0	2.2–139.0	5.2–84.1	
SHBG (nmol/L)				0.9
Median (IQR)	34 (24–42)	32 (26–42)	34 (23–41)	
Range	15.0–74.0	6.0–90	10.0–85.0	
Prolactin (ng/mL)				0.6
Median (IQR)	8.8 (6.5–11.8)	8.5 (6.2–12.1)	8.3 (6.4–11.2)	
Range	3.7–19.8	1.0–17.0	2.5–17.0	

Values are presented as number (%) otherwise indicated.
IQR: interquartile range, LBW: low birth weight, NBW: normal birth weight, HBW: high birth weight, BMI: body mass index, CCI: Charlson Comorbidity Index, FSH: follicle-stimulating hormone, LH: luteinizing hormone, InhB: Inhibin B, tT: total testosterone, E_2: estradiol, SHBG: sex hormone-binding globulin.
[a]p-value according to chi-square test or the Kruskall–Wallis test, as indicated; [b]p<0.01 *vs* LBW group.

HBW groups. Moreover, infertile men with LBW had higher SDF and worse ART outcomes compared to patients in the other groups. LBW status emerged to be associated with pathologic SDF and negative ART outcomes, after accounting for known confounders.

In terms of clinical parameters, we showed that

Table 3. Seminal characteristics of infertile patients according to birth weight

	LBW	NBW	HBW	p-value[a]
No. of patients (n=1,063)	79 (7.5)	807 (76.0)	177 (16.5)	
Semen volume (mL)				0.6
Median (IQR)	3.0 (1.5–3.5)	3.0 (2.1–4.0)	3.0 (2.0–4.0)	
Range	0.2–8.0	0.5–10.0	0.5–10.0	
Sperm concentration ($\times 10^6$/mL)				0.2
Median (IQR)	18.5 (3.2–50.0)	19.4 (5.4–51.0)	19.2 (5.5–55.8)	
Range	0.5–204.4	1.1–305.9	0.5–306	
Sperm concentration ≤16$\times 10^6$/mL	36 (45.5)	362 (44.8)	80 (45.1)	0.3
Progressive motility (%)				0.01
Median (IQR)	20 (8–36)	26 (14–41)[b]	25 (11–40)[b]	
Range	0–70	0–96	0–76	
Progressive motility ≤30%	46 (58.2)	406 (50.3)	90 (50.8)	<0.01
Normal morphology (%)				0.03
Median (IQR)	2 (1–6)	4 (1–8)[b]	4 (1–8)[b]	
Range	0–100	0–98	0–99	
Normal morphology ≤4%	47 (59.5)	335 (41.5)	80 (45.1)	0.01
SDF (%)				<0.01
Median (IQR)	45.7 (26.6–59.5)	29.8 (13–50)[b]	24 (18–45)[b]	
Range	9.8–96.4	0.5–100.0	2.0–90.0	
SDF >30%	55 (69.6)	413 (51.1)	77 (43.5)	0.01
Assisted-pregnancy rate (n=282)	11/42 (26.1)	64/185 (34.5)	19/55 (34.5)	0.01

Values are presented as numbers (%) otherwise indicated.
IQR: interquartile range, LBW: low birth weight, NBW: normal birth weight, HBW: high birth weight, SDF: sperm DNA fragmentation.
[a]p-value according to chi-square test or the Kruskall-Wallis test, as indicated. [b]p<0.01 *vs* LBW group.

Table 4. Logistic regression models predicting pathologic SDF index and negative ART outcomes

	SDF >30%				Negative ART outcomes			
	UVA model		MVA model		UVA model		MVA model	
	OR (95% CI)	p-value	OR (95% CI)	p-value	95% CI	p-value	95% CI	p-value
Age	1.12 (0.84–1.34)	0.2	1.11 (0.81–1.36)	0.3	1.16 (1.02–3.54)	0.02	1.20 (1.08–4.02)	0.02
LBW	4.18 (1.82–6.83)	0.001	3.72 (1.91–7.49)	<0.001	3.21 (1.24–9.87)	0.01	2.29 (1.13–8.84)	<0.001
CCI≥1	1.01 (0.91–1.11)	0.6	1.02 (0.89–1.24)	0.7	1.01 (0.76–1.32)	0.7	1.01 (0.54–1.32)	0.7
FSH	2.36 (1.16–4.45)	<0.001	1.85 (1.11–5.34)	<0.001	1.11 (0.91–1.98)	0.3	1.10 (0.95–2.09)	0.5
Testicular volume	-0.37 (-0.82–0.85)	0.1	-0.48 (-0.84–1.09)	0.2	-0.56 (-0.67–1.07)	0.7	-0.77 (-0.94–1.15)	0.9
Varicocele	1.01 (0.93–1.13)	0.4						
SDF >30%	–		–		3.32 (2.09–9.45)	0.001	2.99 (2.10–10.19)	<0.001
Partner's age					1.35 (1.15–4.76)	0.001	1.34 (1.12–5.02)	0.001

UVA: univariante, MVA: multivariante, ART: assisted reproductive technology, LBW: low birth weight, CCI: Charlson Comorbidity Index, FSH: follicle-stimulating hormone, SDF: sperm DNA fragmentation.

LBW men had smaller TV along with lower testosterone levels but higher FSH values, compared with those in the other groups. As a whole, the current findings corroborates previous evidence in support of the hypothesis that BW has an impact on gonadal function in postnatal life [20]. In this context, Cicognani et al [40] showed that individuals born small for gestational age (SGA) had a pituitary-gonadal axis that tends toward hypogonadism; moreover, various studies have shown increased serum FSH levels in SGA boys [41].

Conflicting data exists in the current literature regarding the impact of BW on conventional semen

parameters. Faure et al [22] analyzed data from 92 subfertile men and showed a positive association between total sperm count and BW. Subsequently, a larger cross-sectional study analyzed the impact of different BW categories on clinical and conventional semen parameters in 827 infertile men. Authors reported that participants with LBW showed reduced sperm motility and reduced rates of normal sperm morphology compared to NBW and HBW men [20]. Conversely, other Authors failed to find any association between BW and sperm quality [21,23]. Our results corroborate the negative impact of LBW on conventional semen parameters. Previous preclinical studies have suggested that maternal environment may impair Sertoli cell development and number, thus contributing to a negative impact on subsequent fertility in adulthood [42]. Although BW represents only a surrogate of the intrauterine factors acting on the development of the gonadal system, it can be speculated that it may have an influence toward semen quality in adulthood.

SDF refers to single and double-stranded DNA breaks in the mature male gamete, which can lead to impaired fertility and reproductive outcomes when they accumulate [43]. Also in consideration of the limited effectiveness of the macroscopic data provided by semen analysis [44], SDF testing has become an important tool for the clinical management of infertile couples either in terms of diagnostic purposes or to guide future therapeutic decisions [1,3]. Different molecular mechanisms that impair sperm DNA integrity have been described, thus including abortive apoptosis, defective repair of DNA breaks and oxidative stress [45]. However, the impact of BW on sperm DNA integrity has been scantly analyzed. Faure et al [22] showed a positive correlation between BW and sperm fragmentation ($r=0.19$, $p=0.004$) in subfertile men; on the contrary, Whitcomb et al [21], in a cohort of 427 male participants from the Longitudinal Investigation of Fertility and the Environment population-based study, reported that SDF was significantly higher in men with LBW (22%) compared to men reporting either NBW (6%) or HBW (7.6%). In our study relying on infertile participants only, SDF was significantly more impaired in LBW men as compared with NBW or HBW. Moreover, LBW emerged as an independent predictor of pathologic SDF scores, after accounting for relevant clinical confounders. Once again it could be speculated that those prenatal factors which are known to impact on gonadal function and development in adulthood, they might also contribute to the dysregulated genetic and epigenetic conditions that are associated with impaired sperm DNA integrity.

It is known that the risk of LBW is higher with female causes of infertility (ovulatory disorders, tubal disorders and endometriosis) compared to unexplained infertility or MFI, after ART treatments [46]. However, whether being born with LBW could affect ART outcomes is still unknown. Liffner et al [19], in their Swedish population-based registry study, analyed data from 21,353 participants attending IVF clinics. They found that men born SGA were more likely to have needed donated spermatozoa to become fathers and were more likely to have used ICSI than men born appropriate for gestational age. No differences in the total number of ART treatments or in the number of ART treatments needed to achieve the first delivery of a child were noted [19]. Our results show that the ART pregnancy rate was lower in LBW compared to both NBW and HBW categories (26.1% *vs.* 34.5% *vs.* 34.5%, $p=0.01$). Furthermore, LBW men had a double risk of negative ART outcomes compared to those in the other groups, even after accounting for male age, pathologic SDF and partner's age which are recognized strong predictors. Overall these results add to the whole body of evidence suggesting the hypothesis of an association between birth characteristics and male infertility.

Our study is novel since we conducted the first real-life contemporary investigation of the impact of different BW categories on SDF and ART outcomes in a relatively large, homogeneous cohort of infertile men. To this aim, LBW emerged as a strong risk factor for reproductive health, thus suggesting that an appropriate counselling and even preventive measures on fertility potential should be implemented in young adolescents born LBW. Second, after a comprehensive investigation of all participants, we considered only men with pure MFI. In fact, the discrepancy in study outcomes may also be attributable to studies including fertile and infertile men [21,22].

Our study is not devoid of limitations. First, this investigation was a single center study, raising the possibility of selection biases; therefore, future studies are needed to externally validate our results. Second, although the study provides original and novel findings, our relatively small cohort of white-European men with precise data in terms of ART outcomes could

limit the meaningfulness of the findings themselves. Lastly, we were unable to collect data about gestational age which could have an impact on male fertility and ART outcomes.

CONCLUSIONS

This cross-sectional, real life study showed that LBW was associated with impaired clinical and semen characteristics in infertile men compared to both NBW and HBW. SDF and ART outcomes were significantly worse in the LBW group. These data confirmed that disrupted embryonic programming and gonadal development during fetal life in men might impaired future reproductive health. Further studies are needed to externally validate current observations.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: LB, AS. Data curation: EP, PC, GF, FB, CC, MR, SC, AA, FM, LC, LP. Formal analysis: LB. Investigation: LB, AS. Methodology: LB, AS. Project administration: All authors. Supervision: AS, FM, LP. Validation: All authors. Writing – original draft: LB. Writing – review & editing: LB, AS.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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