

Original Research

Prevalence of Low and High BMI in Patients with Infertility

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Abstract

Background: The number of individuals who are underweight as well as overweight is increasing worldwide and is known to lead to menstrual disorders and subfertility. Data regarding the prevalence of infertility in Austrian women are lacking. This study aimed to determine the prevalence of a pathologically low and high body mass index (BMI) in Austrian patients with infertility and to evaluate the live birth rate (LBR) after assisted reproductive technologies (ARTs) compared with normal weight patients. **Methods:** A total of 585 couples with infertility who sought treatment at a single center between April 2017 and April 2019 were included in this retrospective study. The patients were categorized into study group 1 (BMI <19 kg/m², n = 35), study group 2 (BMI >30 kg/m², n = 40), and control group (BMI 19–30 kg/m², n = 95). They were randomly selected from the n = 522 women within these BMI values). **Results:** The prevalence rates of BMI <19 kg/m² and BMI >30 kg/m² were 5.9% and 6.7%, respectively. Baseline clinical and laboratory characteristics as well as the prevalence of pathospermia in their male partners were similar in all study groups. In women undergoing ART (n = 112), LBR was comparable between the study groups (27.3% vs. 31.9% and 22.2%, p = 0.4). **Conclusions:** The prevalence of low and high BMI in Austrian patients seeking fertility treatment was almost 13%. Although LBR was not reduced, physicians should be more attentive to the BMI values of patients with infertility because pregnancy-related complications are linked to being underweight and obese.

Keywords: infertility; underweight; obesity; prevalence

1. Introduction

Globally, infertility is estimated to affect 5%–15% of all couples during their reproductive years [1]. The American Society for Reproductive Medicine (ASRM) defines infertility as a couple's inability to conceive after a period of 12 months of regular unprotected intercourse [2,3]. Female factors have been identified in 33%–41% and male factors in 25%–39% of the affected couples, whereas shared factors and factors of unknown origin account for 9%–39% of the cases [4,5].

Overweight and obesity are becoming more prevalent in both men and women and often coexist with hypertension and insulin resistance (metabolic syndrome) [6]. According to a health survey in 2014, 39% of all Austrian women had a body mass index (BMI) of >25 kg/m² and 13.2% had a BMI of >30 kg/m², which are classified according to the World Health Organization (WHO) criteria as overweight and obesity, respectively [7,8]. Several studies evaluating the impacts of obesity on fertility have shown that these are important causes for ovarian dysfunction and endocrine disorders, particularly those pertaining to the hypothalamus–pituitary–gonadal (HPG) axis [9–11]. Alterations in sexual steroids (androgens and estrogens) and sex hormone-binding globulin (SHBG) as well as reduced levels of gonadotropin-releasing hormone (GnRH), insulin resistance, or hyperinsulinemia are more prevalent in pa-

tients with obesity than in those with normal BMI. Clinically, women with obesity suffer more often from irregular or anovulatory menstrual cycles than those with normal weight [9–12]. If they get pregnant despite these alterations, overweight and obese women present a higher risk of gestational diabetes, pre-eclampsia, fetal macrosomia, and birth complications, such as shoulder dystocia and caesarean section [13–16].

Being underweight (BMI <18.5 kg/m²), on the contrary, is more often associated with hypothalamic disturbances, such as disrupted GnRH pulsatility and low gonadotropin release, which result in amenorrhea. This issue is mainly caused by chronic energy deficiency leading to low leptin levels. Leptin serves as a feedback marker for energy stores in adipose tissues [17,18]. If they get pregnant, underweight women have a higher risk of preterm delivery and of having children with a low birth weight [13,19].

With regard to infertility treatments, high BMI (>30 kg/m²) has been reported to be associated with a longer duration of hormonal stimulation (approximately 11 days vs. 10 days in women with normal BMI) and higher doses of stimulating agents [20–23].

Some studies have indicated that patients with obesity produced oocytes of inferior quality during assisted reproductive technology (ART) cycles and had lower clinical pregnancy rates (CPRs) [24,25]. In comparison, underweight patients have been reported to exhibit no significant



differences in oocyte quality or CPR during ART cycles compared with women of normal BMI [20,24,25].

This study aimed to determine the prevalence of pathological BMI in women trying to conceive who were treated at the University Hospital for Gynecological Endocrinology and Reproductive Medicine, Medical University Innsbruck between April 2017 and August 2020. Furthermore, the impact of BMI on menstrual cycle, laboratory parameters, infertility duration as well as treatment characteristics and outcomes in terms of CPR and the live birth rate (LBR) were investigated. To the best of our knowledge, this is the first study to analyze the prevalence of pathological BMI in patients with infertility in Austria as well as their baseline characteristics, treatment features, and outcomes.

2. Materials and Methods

2.1 Study Population

A total of 958 couples with infertility who presented for their first appointment to the university hospital for Gynecological Endocrinology and Reproductive Medicine, Medical University Innsbruck, Austria, between April 2017 and April 2019 were included in this retrospective study. Couples with female age ≥ 40 years were not included. As shown in Fig. 1, 361 of these 958 infertile couples were excluded because of missing information on BMI and/or because they did not undergo any infertility treatment during the study period. The remaining patients ($n = 597$) who underwent a standardized diagnostic workup and at least one cycle of infertility treatment were categorized into two study groups and a control group based on female BMI. Study group 1 ($n = 35$) comprised women with a BMI of $< 19 \text{ kg/m}^2$ and study group 2 ($n = 40$) comprised women with a BMI of $> 30 \text{ kg/m}^2$. From all women with a BMI of $19\text{--}30 \text{ kg/m}^2$ ($n = 522$), which is considered normal, 95 patients were randomly selected to constitute the control group.

Inclusion criteria were infertility, infertility treatment, female age 18 to 39 years, and known BMI. Exclusion criteria were female age 40 years or older, missing BMI information, no infertility treatment.

2.2 Procedures

Demographic data, including female age, BMI at first presentation and at start of infertility treatment, laboratory values including hormonal and metabolic parameters, as well as the administered infertility treatment and its outcome were manually extracted from the patient's electronic medical record. If any of the variables could not be obtained, they were considered missing. The BMI at first presentation was obtained anamnestically, and in cases where it seemed inconsistent, weight and height were measured.

All couples underwent a standardized diagnostic work-up, including two hormonal analyses during one menstrual cycle (follicular and luteal phases), sonographic and/or laparoscopic tubal evaluation, and two semen anal-

yses. Pathospermia was diagnosed if at least one parameter (concentration and/or progressive motility and/or morphology) was pathological in both semen specimens according to the WHO criteria [26]. Those with normal female BMI were directly offered infertility treatment, including ovarian stimulation either with low dose gonadotropins or with clomiphene citrate for timed sexual intercourse or intrauterine insemination as well as ART, such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), according to the results of the diagnostic workup. Women with infertility who had a BMI of $< 19 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$ were first counselled to aim for a normalization of their body weight.

2.3 Statistical Analysis

Patient characteristics were summarized using mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and percentages for categorical variables. To determine significant differences among the three study groups, nonparametric tests were used because the data were not normally distributed. Fisher's exact test (categorical variables) and Kruskal–Wallis test (continuous variables) were applied. All analyses were performed using the R programming language (version 4.0.5, R-foundation, Vienna, Austria) on Mac.

3. Results

A total of 170 couples met the inclusion criteria (Table 1). According to female BMI, 35 of these were allocated to study group 1, 40 to study group 2, and 95 to the control group (Fig. 1). The prevalence of low BMI in our study population was 5.9%, whereas that of high BMI was 6.7%. The baseline characteristics of the study groups were comparable, except for gravidity and parity, which were significantly higher in group 2 ($p = 0.001$ and $p = 0.01$, respectively) (Table 1). With a median infertility duration of 3 years (IQR 2, 6.5) study group 2 showed a longer period of infertility before first presentation than the other groups, although this difference was not statistically significant. Of the underweight patients, only two reported a known eating disorder.

In women with low and high BMI, a tendency toward a higher prevalence of polycystic ovarian syndrome (PCOS) diagnosed according to the Rotterdam criteria was observed [27] compared with women of normal weight. Although not statistically significant, this was most pronounced in women with obesity. Accordingly, overweight women showed clinical signs of hyperandrogenemia (acne, hirsutism, and effluvium) more often than underweight women. Although cardiovascular comorbidities were more frequent in patients with obesity, hypothalamic ovarian insufficiency was observed more often in underweight patients but did not reach statistical significance.

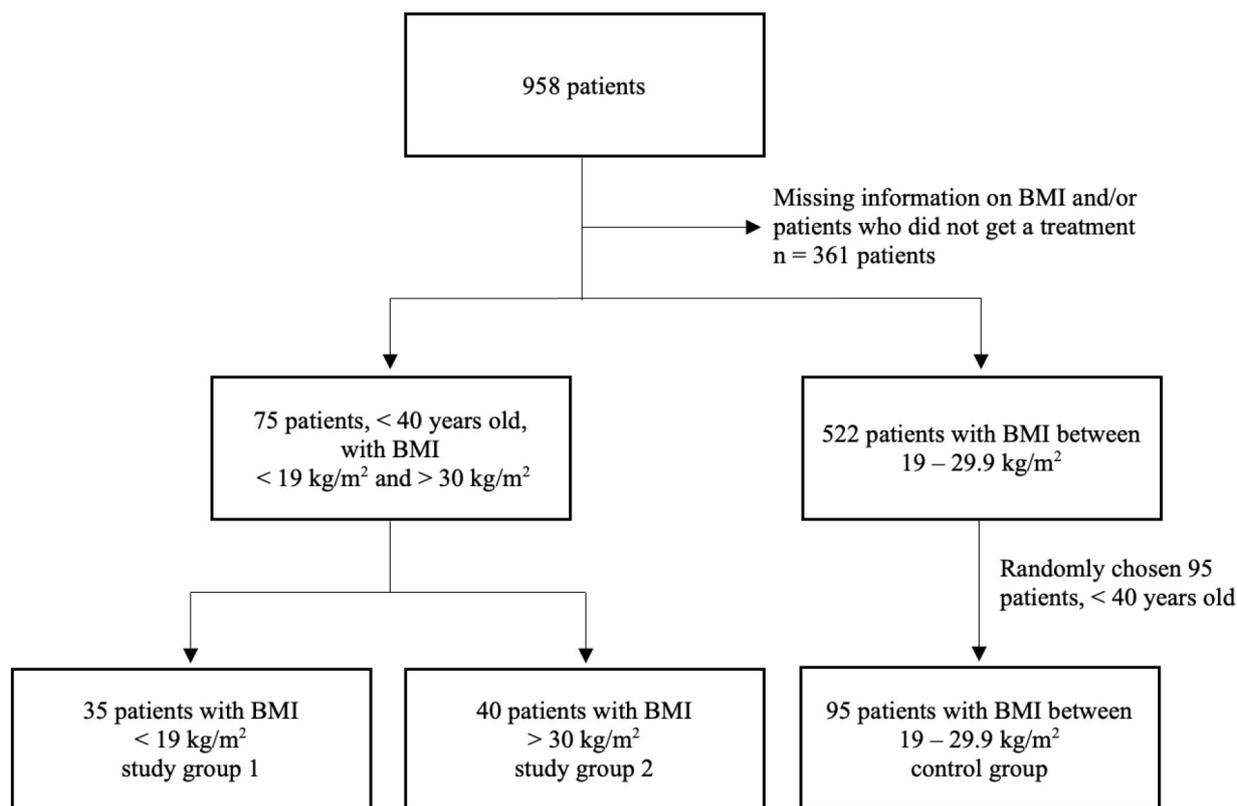


Fig. 1. Inclusion and exclusion of patients in the study.

Baseline hormone levels, such as gonadotropins, estradiol, androgens, and anti-Mullerian hormone (AMH) did not differ significantly in the study population. Clinically, menstrual cycle disorders were tendentially more frequent in women with pathological BMI. While 36% of women with low BMI and 31.6% of those with high BMI reported irregular cycles, only 28.7% did so in the control group ($p = 0.756$). The prevalence of oligomenorrhea and amenorrhea was the highest in study group 1.

Considering the male partners of the women in our study population, the prevalence of pathospermia was comparable among the study groups and the control group.

Couples were offered infertility treatment according to the results of the diagnostic workup. However, in this study, the focus was on ART cycles (Table 2). Overall, 112 patients underwent at least one cycle of controlled ovarian stimulation (COS); 22 patients in study group 1, 27 in study group 2, and 63 in the control group). Altogether, in study group 1, 29 cycles of COS were performed, compared with 35 cycles in study group 2 and 110 cycles in the control group. Of these, 12 cycles (41.4%) were followed by a fresh embryo transfer in study group 1, 16 (45.7%) in study group 2, and 52 (47.3%) in the control group. In the remaining cycles, all resulting embryos were frozen owing to ovarian hyperstimulation syndrome or other reasons. The average number of COS cycles per couple was 1.32 ± 0.65 in study group 1

compared with 1.3 ± 0.47 in study group 2 and 1.75 ± 1.4 in the control group ($p = 0.480$).

Of the patients undergoing ART, 32 underwent at least one frozen–thawed embryo transfer (FET) in study group 1, 31 in study group 2, and 74 in the control group. Accordingly, the mean number of FET per patient was 1.68 ± 1.11 in study group 1, 1.63 ± 0.96 in study group 2, and 2 ± 1.15 in the control group ($p = 0.485$).

Summing up the number of fresh embryo transfers after COS and FETs, overall, 44 embryo transfers were performed in study group 1, 47 in study group 2, and 126 in the control group, which resulted in CPRs of 38.6% ($n = 17$), 46.8% ($n = 22$), and 41.3% ($n = 52$), respectively. The odds ratio for obtaining a clinical pregnancy was 0.90 [0.44–1.80] for women with low BMI and 1.25 [0.64–2.46] for those with high BMI. The LBR was comparable among the three BMI groups and amounted to 27.3% ($n = 12$), 31.9% ($n = 15$), and 22.2% ($n = 28$), respectively. The odds ratio for obtaining a live birth was 1.31 [0.58–2.84] for women with low BMI and 1.64 [0.77–3.43] for those with high BMI.

When the characteristics of the first COS cycles were compared (Table 2), patients with high BMI required a significantly longer stimulation (12 days [IQR 11, 15] vs. 12 days [IQR 10, 13] and 11 days [IQR 9, 13], $p = 0.021$) than those with normal BMI. The median daily gonadotropin dose was comparable, but owing to the longer duration of

Table 1. Baseline characteristics of the three study groups.

Characteristics	Study group 1	Study group 2	Control group	<i>p</i> value
	BMI <19 kg/m ²	BMI >30 kg/m ²	BMI 19–29.9 kg/m ²	
Patients, n	35	40	95	
Age (years)	30 [27, 33.5]	33 [28.5, 35]	32 [28, 36]	0.178
BMI (kg/m ²) at first consultation	18.16 ± 0.73	33.27 ± 2.65	22.77 ± 2.93	<0.001*
BMI stimulation ^o	18.28 ± 0.86	33.46 ± 2.11		
Infertility duration (years)	1.4 [1, 2]	3 [2, 6.5]	2 [1, 3]	0.001*
Gravidity	0.29 ± 0.57	0.95 ± 1.26	0.26 ± 0.57	0.001*
Parity	0.17 ± 0.45	0.42 ± 0.59	0.17 ± 0.4	0.01*
Number of miscarriages	0.06 ± 0.24	0.15 ± 0.36	0.05 ± 0.22	0.136
Known eating disorder	2 (5.7%)	0	0	
Smoking	10 (28.6%)	8 (20%)	17 (17.9%)	0.409
Endometriosis	6 (17.1%)	6 (15%)	13 (13.7%)	0.840
PCOS	10 (28.6%)	13 (32.5%)	5 (5.3%)	<0.001*
Irregular menstrual cycles	9 (36%)	12 (31.6%)	25 (28.7%)	0.756
Hyperandrogenism	2 (5.7%)	6 (15%)	12 (12.6%)	0.427
Cardiovascular co-morbidities	0	2 (5%)	2 (2.1%)	0.505
Partner with pathospermia	6 (20%)	14 (35.9%)	25 (34.7%)	0.281
FSH (U/L)	6.8 [4.9, 8.4]	6.3 [5.1, 7.7]	6.1 [5, 7.8]	0.564
LH (U/L)	6.4 [4.6, 8.9]	5.2 [3.7, 6]	5.1 [3.6, 7.2]	0.143
Estradiol (ng/L)	52 [37, 83]	47 [31.5, 59]	55 [38, 80.3]	0.386
Testosterone (µg/L)	0.28 [0.2, 0.4]	0.28 [0.2, 0.3]	0.25 [0.2, 0.3]	0.398
AMH (µg/L)	3.68 [2, 6.1]	2.69 [1.1, 4.6]	2.48 [1.3, 4.8]	0.229

BMI, Body Mass Index (kg/m²); PCOS, polycystic ovarian syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone.

**p* < 0.05.

^o of the 87 patients with BMI <19.5 kg/m² or >30 kg/m².

Data are presented as mean ± SD, median (IQR = interquartile range), and frequency (percentages).

stimulation, patients in study group 2 required a higher total gonadotropin dose. The number of mature oocytes (MII oocytes) and good quality embryos obtained in the first cycle did not differ significantly among the groups.

4. Discussion

In this study, the prevalence of pathological BMI values in Austrian patients with infertility was determined to be 5.9% for a BMI of <19 kg/m² and 6.7% for a BMI of >30 kg/m².

Overweight women showed higher gravidity and parity when first presenting to our center for fertility treatment. All other baseline demographic as well as clinical and laboratory characteristics were comparable for the various BMI categories. However, PCOS and menstrual cycle disorders tended to be more frequent in women with low and high BMI. The prevalence of pathospermia in the male partners was comparable in all study groups. In women undergoing ART, CPR and LBR were comparable among the three BMI classes. In the first cycles of COS, a longer duration of stimulation as well as a higher total gonadotropin dose was observed in women with BMI >30 kg/m². The number of MII oocytes and good quality embryos obtained in the first cycle did not differ among the groups.

The prevalence of underweight in our patients with infertility is comparable to that described in the general Austrian female population, which is 10.3% in women aged 15–29 years and 4.8% in those aged 30–44 years [7]. These percentages are slightly higher than the ones reported in our neighboring country Germany, where the prevalence of underweight is 4.9% for women aged 18–29 years and 4.4% for those aged 30–39 years [28]. In the general European female population aged ≥18 years, the prevalence of underweight has been reported to be 3.1% [29]. As these data encompass a wide age range, the apparently lower percentage can be explained by the increase in BMI typically observed in advancing age [30,31]. Globally, 9.4% of women aged ≥18 years have been reported to be underweight [32]. The prevalence of BMI >30 kg/m² noted in our study is comparable to that reported for the general Austrian female population. In fact, 5.7% of Austrian women aged 15–29 years and 9.1% of those aged 30–44 years have been reported to have a BMI of >30 kg/m² [7]. In Germany, the reported prevalence in women of reproductive age is higher (9.6% in those aged 18–29 years and 17.9% in those aged 30–39 years). It is, therefore, not surprising that the prevalence of overweight and obesity has been reported to be as high as 36% in pregnant women in Germany [28]. Furthermore, in

Table 2. Number and characteristics of performed ART cycles.

	Study group 1	Study group 2	Control group	<i>p</i> value
	BMI <19 kg/m ²	BMI >30 kg/m ²	BMI 19–29.9 kg/m ²	
n (patients) COS	22 (62.9%)	27 (67.5%)	63 (66.3%)	
n (COS cycles)	29	35	110	
n (fresh transfers after COS)	12 (41.4%)	16 (45.7%)	52 (47.3%)	0.861
COS cycles per patient	1.32 ± 0.65	1.3 ± 0.47	1.75 ± 1.4	0.480
n (patients) FET	32 (91.4%)	31 (77.5%)	74 (77.9%)	
FETs per patient	1.68 ± 1.11	1.63 ± 0.96	2 ± 1.15	0.485
n (transfers total fresh + FET)	44	47	126	
CPR	17 (38.6%)	22 (46.8%)	52 (41.3%)	0.742
LBR	12 (27.3%)	15 (31.9%)	28 (22.2%)	0.381
First COS cycle characteristics				
Stimulation duration (days)	12 [10, 13]	12 [11, 15]	11 [9, 13]	0.021*
Gonadotropin dose daily (units)	186.3 [152.1, 225]	225 [192.5, 225.8]	225 [175, 225]	0.335
n of MII oocytes	10 [9, 14.5]	10 [4, 16]	9 [5, 14.8]	0.640
n of good quality embryos	2.5 [2, 5]	3 [1, 5]	2.5 [1, 5]	0.843

ART, assisted reproductive technology; BMI, Body Mass Index (kg/m²); COS, controlled ovarian stimulation; FET, frozen–thawed embryo transfer; CPR, clinical pregnancy rate; LBR, live birth rate.

**p* < 0.05.

Data are presented as mean ± SD, median (IQR = interquartile range) and frequency (percentages).

comparison with European and worldwide data that approximately 15% of women aged ≥18 years are overweight, the prevalence in Austria is lower both in the general female population and in women seeking fertility treatment [29,33].

The higher baseline gravidity and parity observed in women with a BMI of >30 kg/m² could possibly be explained by the weight gain after previous pregnancies and childbirths. Several studies have reported that women who are already overweight during their first pregnancy show a more pronounced gestational and postpartum weight gain [31,34–36]. As overweight and obesity themselves are causally related to infertility [37], this might explain why patients who were overweight and obese in our study suffered more often from secondary infertility than their normal-weight counterparts. When presenting to our fertility center, they had been unsuccessfully trying to conceive for a longer period than those with low and normal BMI. A possible explanation is that having achieved one or more pregnancies in the past, they might have been more optimistic about their fertility and, therefore, delayed seeking assistance.

Conventionally, PCOS has been associated with obesity. A meta-analysis by Lim *et al.* [38] reported that women with obesity have an odds ratio of 2.77 for the development of PCOS compared with women of normal weight. Accordingly, other studies have documented a pathologically high BMI in 38%–88% of women with PCOS [39]. In line with these findings, we found a tendentially higher prevalence of PCOS in women with high BMI. However, in women with low BMI too, PCOS was more frequent than that in the controls. So far, few studies have examined the

prevalence of underweight in patients with PCOS. Contrary to our results, Anastasiou *et al.* [40] found that only 1.5% of the 1269 women with PCOS were underweight. Further studies are, therefore, needed to clarify the relationship between low BMI and PCOS.

In accordance with previous studies [41–44], our patients with low and high BMI presented with menstrual cycle disorders more frequently than those with normal BMI, although the difference was not statistically significant. This observation is pathophysiologically plausible as both hypoleptinaemia due to diminished fat stores and hyperleptinaemia due to obesity have been reported to suppress the HPG axis [45], thus leading to oligomenorrhea and amenorrhea and, consequently, subfertility.

Only two patients with a BMI of <19 kg/m² (5.7%) reported having suffered from an eating disorder in the past, whereas none of the patients with normal or high BMI did so. Moreover, there were no cases of self-reported current eating disorder in our study population. Patients with eating disorders tend to deny their symptoms. Moreover, no specific diagnostic questionnaires are routinely used in our center. Hence, our data might underestimate the prevalence of eating disorders. However, a recent systematic review on eating disorders in women seeking fertility treatment reported prevalence rates of 1.4%–27.5% for past eating disorders and 0.5%–16.7% for current eating disorders [46]. Considering the small size of our sample, the observed numbers are reasonable.

As we considered a BMI of <19 kg/m² as underweight, the median BMI in this group was 18.28 kg/m². This relatively high median value might explain why our underweight patients exhibited hormone levels comparable

to those of normal weight and obese individuals. In accordance with a large retrospective study assessing the influence of BMI on AMH levels in women without PCOS [47], AMH levels in our study population were comparable in all BMI categories.

With regard to the ART cycles (fresh embryo transfers and FETs) performed in our study population, we found that CPR and LBR were similar for all three study groups. In case of patients with low BMI, our results are in line with two recently published systematic reviews [48,49] and a large retrospective cohort study [50]. For overweight women and those with obesity, however, several previous studies have reported a lower LBR [24,49,51–55]. A recent meta-analysis observed a nonlinear association between BMI and LBR, with a relatively flat curve over a broad BMI range of 16–30 kg/m². In the present study, the mean BMI values of all study groups were within this range, possibly explaining why LBR did not differ significantly among our study groups [56].

To avoid bias due to adaptation of treatment protocols according to the results of the first COS cycle, the characteristics of the first COS cycle were evaluated separately. In accordance with previous studies [57,58], we found a significantly higher duration of stimulation and total gonadotropin dose in patients with obesity. However, the number of MII oocytes and good quality embryos was not reduced in patients with obesity. The literature regarding these outcome measures in patients with obesity is conflicting, possibly because some authors have reported on several treatment cycles whereas others have reported on first treatment cycles only [21]. Further studies are, therefore, required.

Owing to the retrospective design of the present study, data regarding obstetric complications were not available. Nonetheless, previous studies have described an association between low or high maternal BMI and the risk of several pregnancy-related complications. A meta-analysis estimated that 23.9% of any pregnancy complication could be attributed to maternal overweight/obesity. The study found higher risks of gestational hypertensive disorders, gestational diabetes, and large for gestational age at birth in women who were overweight and obese. The risk of preterm birth has been shown to be increased in women with low as well as high BMI [59]. Underweight mothers have also been reported to have increased odds for small for gestational age infants [60]. These studies did not specifically refer to pregnancies from ART, but recent studies have observed similar results for ART pregnancies [61]. As being underweight and overweight often lead to infertility, fertility specialists should be aware not only of the possible difficulties during ART but also of the high risk of obstetric complications in these patient groups. Hence, emphasis should be placed on preconception counselling and adequate prenatal care.

To the best of our knowledge, this is the first study

to evaluate the prevalence of pathologically low and high BMI in patients with infertility in Austria. However, our study is limited by the retrospective design, small sample size, limited observation period, and single-center design. Hence, further studies in other Austrian centers are needed to confirm the prevalence of pathologically low and high BMI in patients with infertility in Austria.

5. Conclusions

The prevalence of low and high BMI in Austrian patients seeking fertility treatment is over 10%. As a higher risk of pregnancy-related complications has been previously reported and the results regarding LBR are conflicting, fertility specialists should be attentive to BMI values in their patients with infertility issues.

Abbreviations

LBR, live birth rate; ART, assisted reproductive technology; ARSM, American Society for Reproductive Medicine; BMI, body mass index; SHBG, sex hormone-binding globulin; GnRH, gonadotropin-releasing hormone; CPR, clinical pregnancy rate; SD, standard deviation; IQR, interquartile range; COS, controlled ovarian stimulation; OHSS, ovarian hyperstimulation syndrome; FET, frozen-thawed embryo transfer; HPG, hypothalamo-pituitary-gonadal.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ALZ, KR, KF and BT designed the research study. KR and LR collected and analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethics approval: Ethical approval was waived by the local Ethics Committee of the Medical University of Innsbruck (EK: 1272/2019) in view of the retrospective nature of the study and all the procedures being performed being part of routine care. Informed consent was obtained from all individual participants included in the study. Patients signed informed consent for publishing their data.

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Conflict of Interest

The authors declare no conflict of interest.

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