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Research Article

Pregnancy Results with Male Adult-Onset Hypogonadotropic Hypogonadism

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Abstract

Background: Androgen deficiency and infertility lead to male hypogonadism. The main purpose of this study was to evaluate pregnancy outcomes of a cohort of males with adult-onset hypogonadism (AOHH) after gonadotropin treatment with hCG/hMG.

Methods: This retrospective study included 17 patients from a group of 2,340 men referred to Zekai Tahir Burak Women's Health Training and Research Hospital for evaluation of azoospermia. Final sperm concentration, serum luteinizing hormone (LH), follicle stimulating hormone (FSH), endogenous testosterone, and pregnancy rates were compared to baseline, and statistical significance was $p < 0.05$.

Results: The mean LH increased from 0.05 (0 - 0.6) to 0.07 (0.01 - 0.58) IU/liter ($p = 0.59$), and FSH increased from 0.42 (0 - 2.2) to 2.63 (1.48 - 7.03) IU/liter ($p = 0.001$). Mean serum endogenous testosterone increased from 714.4 ng per deciliter, and spermatogenesis was induced in all patients. Five patients who want sharing personal data excluded of the study, and of the remaining 12, pregnancy occurred in 42% (n = 5) of their partners, including 17% (n = 2) with spontaneous pregnancy. Nine of the couples (75%) underwent IVF treatment using intracytoplasmic sperm injection (ICSI) and three of these (25%) became pregnant. One pregnancy ended in spontaneous abortion at 9 weeks of gestation and the other four resulted in the delivery of normal offspring.

Conclusion: Spermatogenesis can be improved by gonadotropin treatment in male AOHH, and although semen quality is low after treatment, pregnancy may still occur in a significant portion of cases.

Keywords: *Male Adult-Onset Hypogonadotropic Hypogonadism; Pregnancy; In Vitro Fertilization*

Introduction

Adult-onset hypogonadotropic hypogonadism (AOHH), defined as testosterone deficiency due to failure of the testicles and/or hypothalamus-pituitary pathway, is a rare cause of male infertility, affecting < 1% of infertile men [1]. AOHH can be defined by low testosterone levels, associated signs and symptoms of hypogonadism, and low or normal serum luteinizing hormone (LH) and follicle stimulating hormone (FSH). It can also be present in healthy adult men after completion of normal pubertal development and often with proven fertility

[1]. It may appear as attenuated virilization/eunuchoidism, decreased libido, decreased spontaneous erections, difficulty maintaining an erection, gynecomastia, infertility, or osteoporosis [2]. The biochemical profile is the same as that of men with congenital gonadotrophin-releasing hormone (GnRH) deficiency. Disruption of GnRH secretion is reflected in LH secretion. Both clinical features coincide with low serum testosterone concentrations and successful response to a physiological regimen of exogenous GnRH replacement in 90% of cases [3]. Mutations of genes expressed in either the hypothalamus or the pituitary gland, including those involved in GnRH development and function, account for only 40% of cases, involving reported mutations in more than 30 genes [4]. AOHH may be caused by various anatomical factors, such as infiltrative and space-occupying lesions [5,6] granulomatous disease, and lymphocytic hypophysitis [6]. Malnutrition, vigorous exercise, medical illness, and pharmacologic agents (e.g. opioids, glucocorticoids, cimetidine, tricyclic antidepressants, chemotherapy, nicotine, marijuana) are other known causes [7]. In some patients, depression or alcohol and/or drug abuse occur, but these disorders are not related to serious prolonged hypoandrogenemia [2]. Magnetic resonance imaging (MRI) and endocrine examinations have not revealed any identifiable causes for hypogonadotropic hypogonadism [8].

Spermatogenesis can be achieved via gonadotropin therapy with human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG), or with purified or recombinant follicle-stimulating hormone (FSH) [2,9]. To stimulate testosterone secretion before hMG, gonadotropin therapy is usually initiated with hCG for 6 - 12 months [10]. The primary efficacy endpoint for clinical reports is a sperm concentration compatible with achieving pregnancy [11,12].

Purpose of the Study

The purpose of the present cohort study was to evaluate pregnancy outcomes for AOHH patients after gonadotropin treatment.

Materials and Methods

Study population

This retrospective study included 17 males aged 26 - 53 years with adult-onset hypogonadotropic hypogonadism, who presented with azoospermia. The patients were identified from a group of 2,340 men referred to the Urology Unit at Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, for evaluation of azoospermia. The study protocol conformed with the principles of the Declaration of Helsinki, and approval of the institutional review board was obtained (Number: 16) Each patient provided informed consent.

AOHH was diagnosed if there was persistent hypogonadism with low LH and FSH. All patients had complete pubertal development by age 18 years. The study group had normal cortisol, thyroid stimulating hormone (TSH), prolactin, and brain imaging on MRI to exclude secondary causes of hypogonadism. The initial diagnostic evaluation of each patient included a physical examination, semen analysis, and blood analyses for gonadotropin and sex steroid concentrations. Physical examination revealed that all patients had both testes inside the scrotum with an adult-sized penis. Testis volume in those that were evaluated was 15 - 20 ml. Besides frankly hypogonadal serum testosterone levels (130 ng/dl) in the presence of low or normal gonadotropins on multiple assessments, the patients had otherwise normal anterior pituitary function and normal ferritin concentrations [13].

The subjects' mean age was 37.8 ± 1.78 years. All patients were referred for the evaluation and treatment of male infertility, and all were azoospermic. After baseline investigations, they started gonadotropin therapy for 18 months with the same treatment protocol. Basal FSH, LH, testosterone, semen volume, and IVF cycle parameters and pregnancy outcomes were recorded before and after the treatment (Table 1-3).

The treatment protocol for all patients was self-administration of urinary-derived hCG (Pregnyl, Orgaxnon, Netherlands) 2 × 1500 IU s.c./week, trailed by combined hCG/hMG (Menagon, Ferring, Italy) 3 × 150 IU s.c./week throughout 3 months. Whilst the hMG levels were continuing constant, the hCG dose was advancing to higher ratios amid abnormal adult range levels of serum testosterone after 6 - 9 months of hCG treatment. Every three months, each patient submitted semen specimens for analysis.

Men with adult-onset hypogonadotropic hypogonadism	Age	Sperm count_10^6/ml	Progressive Motility (%)	Sperm volume (cc)	Testis volume	Serum LH IU/liter	Serum FSH IU/ liter	Serum Testosterone ng/dl
Case1 pre-treatment	37	0	0	2	20	0,07	0,65	19,02
Post treatment		16	34	2.5		0,01	2,64	541,35
Case2 pre-treatment	48	0	0	5	20	0,01	0,4	220
Post. treatment		0,01	30	5		0,07	2,63	788,7
Case3 pre-treatment	26	0	0	0,2	NA	0,01	0,01	35,97
Post treatment		0,001	0	2		0,01	6,65	1047,1
Case 4 pre-treatment	37	0	0	0,5	NA	0,12	0,39	38,65
Post treatment		5	40	2		0,07	1,67	645,19
Case 5 pretreatment	53	0	0	4	20	0,07	1,01	106,37
Post treatment		0,013	16	2,5		0,12	7,03	739,98
Case 6 pretreatment	29	0	0	2,5	20	0,4	1,03	18,98
Post treatment		10,3	38	2,5		0,07	2,32	448
Case 7 pretreatment	32	0	0	0,3	20	0,59	0,65	300
Post treatment		0,008	45	4		0,05	1,84	538,54
Case 8 pretreatment	36	0	0	3,3	25	0,01	0,01	52,7
Post treatment		0,003	37,5	2		0,01	3,22	782
Case 9 pre treatment	46	0	0	1,5	NA	0,01	1,22	166,67
Post treatment		0,001	30	2		0,07	2,23	668.23
Case 10 pre treatment	40	0	0	2	20	0,07	0,3	17,47
Post treatment		0,001	30	2		0,01	3,06	649,29
Case 11 pretreatment	37	0	0	2	15	0,53	1,48	27,82
Post treatment		0,001	0	2		0,58	2,32	589,9
Case 12 pre treatment	30	0	0	2	20	0,07	0,31	195,7
Post treatment		0,004	25	2		0,02	5,21	777,13

Case 13 pretreatment	41	0	0	1,5	NA	0,01	0,42	2,23
Post treatment		0,001	0	2		0,01	2,36	458
Case 14 pretreatment	31	0	0	3	NA	0,01	0,01	53,25
Post treatment		0,004	25	3		0,01	1,84	815,8
Case 15 pretreatment	36	0	0	1,5	15	0,01	2,2	56,89
Post treatment		0,006	30	2		0,09	2,42	446,29
Case 16 pretreatment	47	0	0	5	NA	0,01	0,22	87,44
Post treatment		0,006	50	5		0,07	6,65	1257
Case 17 pretreatment	38	0	0	3,5	25	0,01	0,7	82,32
Post treatment		0,001	30	3,5		0,01	3,48	953
Mean ± SD Pretreatment Post treatment Median (min –max)	37,8 ± 7,36	0 0,012 (0 - 16)	0 30 (0 - 50)	2,3 ± 0,3 2 (2 - 5)	20 (15 - 25)	0,07 (0 - 0,6) 0,05 (0,01 - 0,58)	0,42 (0 - 2,2) 2,63 (1,48 - 7,03)	Mean ± SD 87.15 ± 84.61 714,4 ± 221,2

Table 1*: Sperm and Hormone concentrations in men with adult onset hypogonadotropic hypogonadism before and after the treatment. FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; Testosterone Levels, NA: Not Applicable.*

Inclusion and rejection criteria

The scope of this study does not contain patients experienced previous testicular tumors, radiotherapy, chemotherapy as well as iron overload and primary hypogonadism along with unilateral or bilateral anorchia. Moreover, the patients had functional hypogonadism (due to starvation, both inflammatory bowel and chronic disease) were removed as were those who had taken second or third times of gonadotropins or GnRH as well as those for whom there were inadequate data on compliance with use of gonadotropins (four cases). All patients had no family history of anosmia or visual field defects. None of the patients had children, and all of the female partners were reported to have no chronic medical conditions, with normal menstrual cycles (Table 2 and figure 1).

Spermogram

Semen samples were collected via masturbation in a private room near the laboratory, after three days of sexual abstinence. The specimens were assessed using a computerized semen analyzer for conventional parameters, including sperm motility and sperm concentration (pre-washed for 30 minutes at room temperature) after liquefaction. The standard swim-up method with sperm-preparation media (Ferticult Flushing medium TM, FertiProNV, Beernem, Belgium) was used to process the remainder of the semen. A computer-assisted semen analyzer was used for the post-wash analyses. For quality control, the same andrology laboratory technician performed all of the sperm analyses.

	GnRH Antagonist Protocol							
Women age	39	28	33	32	37	32	26	26
BMI (kg/m^2)	38	23.1	23	30.8	27	36	23.2	28.4
Antral follicle count	6	15	5	6	2	15	8	5
Day 3 FSH level (IU/liter)	6.4	5.1	6.4	7.8	7.7	5.8	8.8	9.9
Day 3 LH level (IU/liter)	2.8	7.7	3.3	4.8	2.2	16.4	5.8	5.9
Day 3 estradiol level (ng/dl)	25.4	52	35.3	34	67	49	30.9	34
Total rFSH administered (IU)	2400	800	600	1800	2400	1050	1000	1600
<14 mm follicle count	4	20	2	2	5	5	6	3
≥ 14 mm follicle count	6	6	7	10	4	10	10	4
Duration of stimulation (days)	9	13	11	9	9	9	7	9
Estradiol level on hCG day (pg/ml)	1084	754	1440	2484	2757	2450	2853	1148
Progesteron levels on hCG day (pg/nl)	0.38	0.9	1.4	0.84	0.53	0.7	1.1	0.8
Endometrial thickness (mm)	10.5	7	7	11	10.4	11	11	8
No of retrieved oocytes	6	5	11	18	8	11	15	5
Number of M2 oocytes collected	2	2	2	5	3	7	5	0
Total embryos collected	2	1	3	5	3	7	4	0
Mean number of transferred embryos	1	1	1	1	2	1	1	0
Transfer day of embryos	3	3	3	3	3	3	3	0
Pregnancy result	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Total Fertilisation Failure

Table 2*: ICSI cycles characteristics the couple of the treatment in men with adult onset hypogonadotropic hypogonadism.*

The clinical relevance of routine semen analysis was achieved according to standard WHO criteria, including the specific reference standards [14]. Testicular volumes were measured using a Prader orchidometer. The endpoint of the study was return of spermatogenesis and pregnancy outcomes. Excess spermatozoa were obtained and cryopreserved for future cycles in all cases.

Statistical analysis

The distributions of all continuous variables for normal or non-normal distributions were tested using the Kolmogorov-Smirnov test. SPSS version 11.5 was used for statistical analysis of the data (SPSS Inc., Chicago, IL, USA). The mean ± standard deviation (for normally distributed data) or median and range (for non-normally distributed data) were derived from the collected data. For normally distributed data, the paired *t* test was used, and for data not passing normality, the Mann-Whitney rank sum test was used for comparing group follow-up data with baseline. The statistical significance level was set at $p < 0.05$.

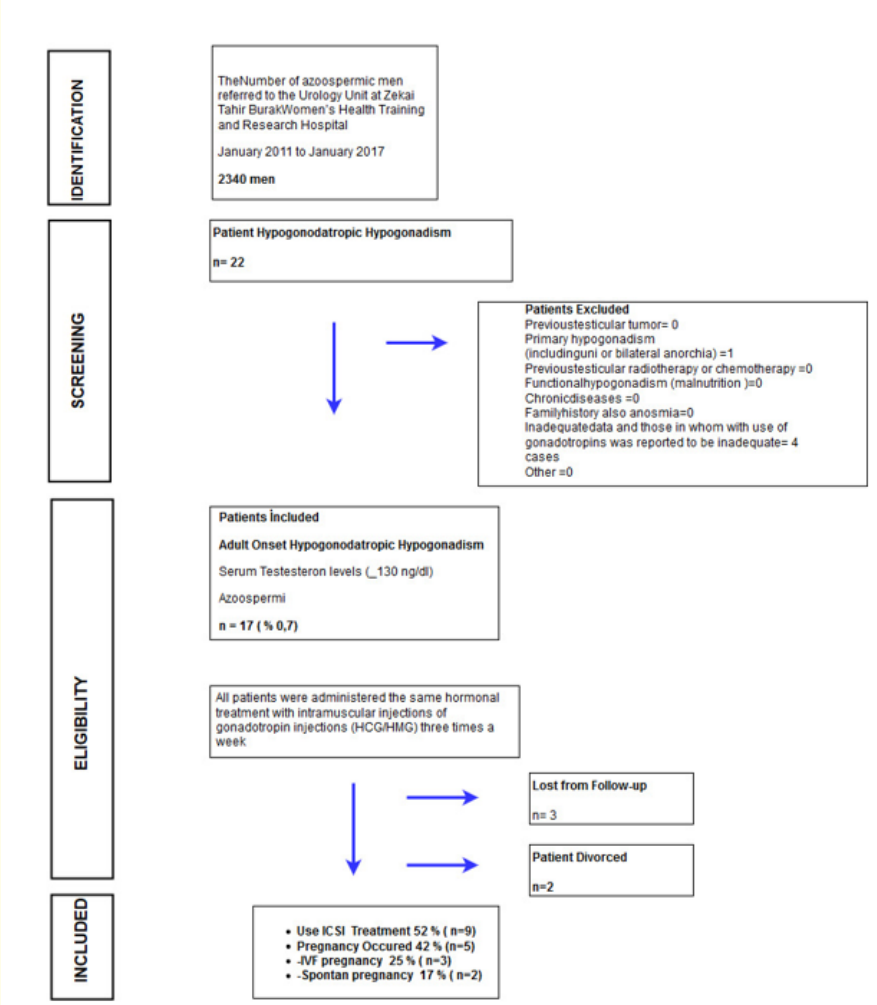

Figure 1: *Study flow chart of retrospective case control study.*

Results

Baseline serum levels of LH, FSH, and testosterone before treatment were 0.07 (0 - 0.06) IU/L, 0.42 (0 - 2.2) IU/L, and 87.15 ± 84.61 (2.23 - 300 ng/ml), respectively. Semen volume was 2.34 ± 0.35 (0.2 - 5) mL. After treatment, serum levels of LH, FSH, and testosterone were 0.05 (0 - 0.06) IU/L, 2.63 (0 - 2.2) IU/L, and 714.4 ± 221.2 (446.2 - 1257 ng/ml), respectively (Table 2 and 3). To achieve fertility, AOH was treated for a median of 16 months (range, 6 - 32) with intramuscular injections of gonadotropin (hCG/hMG) three times a week. After treatment, all patients could ejaculate and had restored spermatogenesis. After treatment, three patients were lost from follow-up and two patients were divorced. In the partners of the remaining 12 men, five pregnancies occurred (42%), including two (17%) natural conceptions and three (25%) after intracytoplasmic sperm injection (ICSI) with IVF (Table 2). One pregnancy ended in spontaneous abortion at nine weeks of gestation and the other four resulted in the delivery of normal offspring.

Variables	Pretreatment		Posttreatment		
	Mean ± SD	Median (Min - Max)	Mean ± SD	Median (Min - Max)	p value
Sperm Volume (cc)	2.34 ± 1.47	2.00 (0.20-5.00)	2.56 ± 1.17	2.00 (1.50-5.00)	0.553
Testis Volume (cc)	5.00 ± 0.79	5.00 (4.00-6.00)	17.94 ± 2.54	20.00 (15.00-20.00)	< 0.001
Serum LH (IU/liter)	0.12 ± 0.19	0.07 (0.01-0.59)	0.08 ± 0.13	0.05 (0.01-0.58)	0.590
Serum FSH (IU/liter)	0.71 ± 0.69	0.42 (0.01-2.22)	3.34 ± 1.85	2.63 (1.48-7.03)	0.001
Serum Testesteron (ng/dl)	87.15 ± 84.61	53.25 (2.23-300.00)	714.44 ± 221.24	668.23 (446.29-1257.00)	< 0.001

Table 3*: Comparisons of secondary outcome values at the start of the treatment phase and the end of treatment.*

Discussion

The principal finding of this randomized, open-label treatment study is that AOHH infertility is a treatable condition, as there were statistically significant differences in semen parameters among patients before and after gonadotropin therapy. The results showed that sequential treatment with HMG affected pregnancy outcomes: pregnancy occurred in 42% of the patients' partners, for a total of 17% with natural conception and 25% with ICSI.

As a treatable form of male infertility, clinical identification of AOHH is important. Spermatogenesis can be achieved via gonadotropin therapy [2,5,7]. Hormonal treatment replaces naturally missing gonadotropins with hCG substituting in a role of LH and FSH, applied either by hMG or rFSH to activate spermatogenesis, inducing gonadal testosterone production. Patients having flawless pituitary function by using minipumps regulate Pulsatile subcutaneous (s.c.) GnRH [1,3,15]. However, GnRH is not often used due to the inconvenience of prolonged, continuous wearing of an external pump [16,17]. Another type of hormonal therapy is recombinant products such as rhFSH and HMG, which contain preparations that stimulate Sertoli cells. Kobori., *et al*. revealed that rhFSH had greater purity than hMG, and that rhFSH in combination with hCG was effective at inducing spermatogenesis in AOHH patients [1]. Bouloux., *et al*. showed that rhFSH (follitropin alpha) at a dose of 150 IU three times weekly was effective at initiating spermatogenesis in the majority of male AOHH patients pretreated with hCG, and treatment was well-tolerated over periods of at least 18 months [18]. In a series of cases of AOHH treated with highly purified FSH and hCG over six months or more, the spermatogenic response was observed in 48 out of 60 patients (80%) [18]. Combination treatment of hCG/hMG has also been studied, showing a positive response rate (i.e., increased sperm count) of between 40% and 70% [18]. However, due to the short half-life of FSH, recFSH or hMG must be injected three times per week for a longer time or at higher doses, for periods of several months to years [15]. Such treatment can be a long, grueling, and costly process that may result in disappointment, along with the discomfort of frequent injections. We preferred hMG to rFSH due to cost as it is relatively less expensive than recombinant therapy. In our study, all patients received the same treatment protocol. Urinary-derived hCG at a dose of 5,000 IU was administered subcutaneously twice per week. After testosterone levels normalized, this was followed by combined hCG/hMG three times at 150 IU s.c. in a week throughout 3 months, which was self-administered by subcutaneous doses. Spermatogenesis develops in most AOHH patients within 18 months of treatment [19]. In our study, spermatogenesis improved within six months of treatment, and the patients were treated for a median of 16 months (range, 6 - 32). In the non-responders, TESE was performed, and testicular specimens revealed that spermatogenesis was arrested early stages. In our study, after treatment all patients could ejaculate, and spermatogenesis was restored. Reasons for not needing TESE may include a lack of cryptorchidism or primary testicular failure.

In the few studies reporting AOHH [17,19-21], the aim of treatment was induction of spermatogenesis to overcome male infertility and/or androgenization. The treatment strategy will depend on the requirements for fatherhood. Following hormonal fertility treatment in hypogonadotropic hypogonadal men, sperm counts are usually below the lower limit of normal range.

Since a wide range of subgroups of patients make pregnant their mates instinctively with underdeveloped sperm concentrations, gonadotropin treatment greatly increased the fertilizing potential of the spermatozoa in our AOHH patients. This case is conforming with previous studies [2,3,15,16]. Spontaneous pregnancies are also known to occur in partners of AOHH patients treated with hCG and FSH, and the use of assisted reproductive technologies, in particular ICSI, would be appropriate for couples wishing to conceive [17,20]. In our study, 17 (n = 2) of the patients' partners had spontaneous pregnancy. Of the nine couples who underwent IVF treatment with ICSI, three become pregnant (25% of the study group). In a study of a similar group of patients, Rohayem., *et al*. [3] reported that 55% impregnated their partners, 18% of whom required ICSI, while conception was spontaneous in 37%. Kobori., *et al*. [1] reported that one in seven patients achieved spontaneous pregnancy, while four others froze sperm for future ICSI. For these patients, 36 months was the longest administration period. Presently, the take-home baby rate was 29% [1]. Bouloux., *et al*. showed that for 26 patients, successful pregnancy was achieved in four out of seven couples who wished to conceive [18]. Warne., *et al*. performed a clinical study on 100 couples, of whom 51 were seeking fertility [10]. A total of 16 pregnancies occurred in 14 partners (27%), which led to the birth of 11 healthy babies. Two biochemical pregnancies were not confirmed on ultrasound, two ended in miscarriage, and the outcome of one pregnancy was lost to follow-up [19]. In agreement with other studies [7-9,15], pregnancy was achieved after hormone replacement treatment in our study, as 25% of patients' partners were pregnant after ICSI treatment and 17% were pregnant spontaneously.

Limitations of the Study

Statistical deductions in our study were restricted by the limited size of the different AOHH subsets. Hence, genetic screening for mutations was not performed due to insufficient funds. Also due to cost, we did not analyze our patients' basal levels of inhibin B, which is a predictor of the testosterone response to hCG. In addition, although pre-treatment testicular size is a predictor of pregnancy [22], we had no records of our patients' pre-treatment testicular volume. Our findings are promising, but in order to establish the optimal treatment approach for AOHH, large multicenter clinical trials will be necessary.

Conclusion

The emerging result from our study is that hormone administration is a first-line treatment for AOHH, and even if semen quality is low, pregnancy may occur in a large number of these cases. Our study also revealed that male adult-onset hypogonadotropic hypogonadism is one of the few treatable forms of male infertility.

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Declaration of Interest

The authors report no support funding for this paper. The authors declare that we are not in any situation which could give rise to conflicts of interest. Article implies that the work described has not been published previously or ethical restrictions.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of ethics of the World medical Association (Declaration of Helsinki).

Confidentiality of Data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Notes on Contributors

Contributed to conception and design. YEU, NY. Acquisition of data: NA, AA, ADT, CG. Contributed to all experimental work, data and statistical analysis, and interpretation of data. AA, NA. Were responsible for overall supervision YEU. Drafted the manuscript, which was revised by YEU. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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