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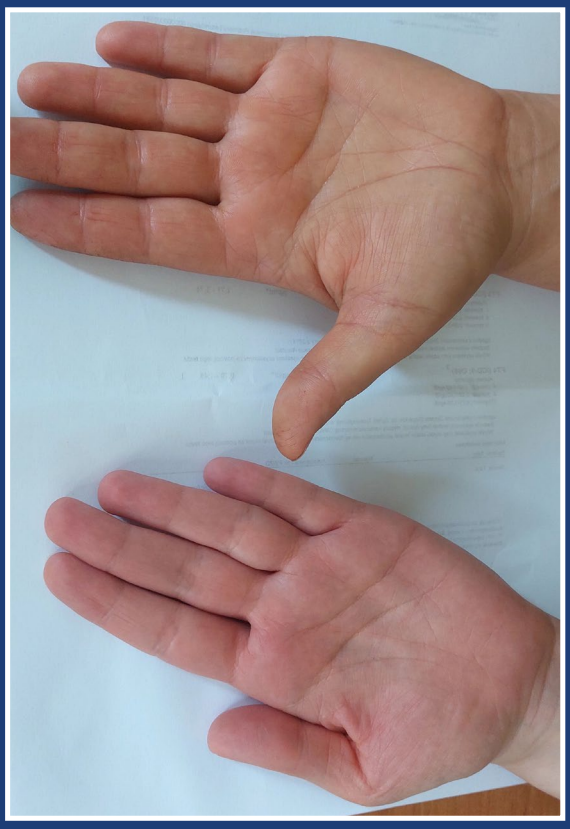

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ORIGINAL RESEARCH PAPER

Underweight and obese women – results of in vitro fertilization

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: Both obese and underweight women with fertility problems often seek help from infertility treatment clinics using the in vitro fertilization (IVF) procedure. The aim of our study was to analyze the results of IVF in obese patients (BMI ≥ 30 kg/m2) and underweight patients (BMI < 18.5 kg/m2) in comparison to patients of normal weight.

Material and methods: This was a retrospective study of underweight (BMI < 18.5 kg/m2) and obese (BMI ≥ 30 kg/m2) women who underwent intracytoplasmic sperm injection (ICSI). The control group consisted of patients of normal weight. In order to exclude the influence of age on the results of IVF, patients in all groups were <38 years old.

Results: Significantly fewer oocytes were obtained from obese patients compared to normal weight patients (8.4±2 vs. 11.3±3). In addition, the lowest numbers of mature oocytes at the metaphase II stage and of blastocysts were obtained from these patients (2.8±0.2 vs. 3.7±0.4a, 4±0.3), and the blastocysts were of worse morphological quality than in the other groups. In obese patients, 17% of cycles were cancelled due to a lack of oocytes or embryos for transfer. There was no difference in the implantation rate in underweight patients compared to those of normal weight (47% vs. 51%), but a lower implantation rate was noted in obese patients (38%).

Conclusions: Obese patients cannot rely on the same effectiveness of IVF as patients of normal weight. However, it seems that underweight patients are in a much better situation, for whom most stages of the in vitro procedure are as effective as in patients of normal weight.

Keywords: obesity, underweight, IVF, implantaion rate, blastocysts

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Introduction

Obesity is recognized by World Health Organization (WHO) as a noncommunicable disease that constitutes a serious health problem worldwide, especially in highly developed countries. According to WHO, obesity occurs when the BMI exceeds 30 kg/m^2, and a person is considered overweight when the BMI exceeds 25 kg/m^2. The effects of obesity include, above all, an increased risk of cancer, diabetes and circulatory system disorders.

Another problem that is common in highly developed countries is infertility, which is also classified by WHO as a noncommunicable disease. Recently, a strong correlation has been demonstrated between these two diseases, i.e. obesity and infertility. Obese women (BMI ≥ 30) experience infertility three times as often as women with a normal BMI [1]. Obesity leads to infertility, among other things, by adversely affecting the functioning of the hypothalamus-pituitary-ovary axis [2]. Increased insulin levels and a tendency towards insulin resistance in obese women are often associated with the occurrence of polycystic ovary syndrome (PCOS) [3]. Obesity also leads to infertility through a direct impact on the quality and metabolism of oocytes [4,5]. The accumulation of lipids in oocytes and surrounding granulosa cells disrupts their functioning and leads to lipotoxicity [6]. Metabolic and endocrine disorders that accompany obesity negatively affect uterine receptivity and embryo implantation. They lead to endometrial disorders and increase the rate of pregnancy complications and miscarriages [6]. The risk of miscarriage increases by 25–37% in obese women [1]. On the other side of the global obesity problem, there is the fashion for a slim figure, and consequently eating disorders and new trends in weight loss leading to rapid reduction in weight and patients remaining underweight (BMI < 18.5 kg/m^2). Being underweight leads to such fertility disorders as impairments to the hypothalamic-pituitary-gonadal (HPG) axis and hormonal imbalances, irregular ovulation, or complete cessation of ovulation and complete cessation of menstruation [7].

Both obese and underweight women with fertility problems often seek help from infertility treatment clinics using the in vitro fertilization (IVF) procedure.

The aim of our study was to analyze the results of IVF in obese patients (BMI ≥ 30 kg/m^2) and underweight patients (BMI < 18.5 kg/m^2) in comparison to patients of normal weight.

Materials and methods

This was a retrospective study of underweight (BMI < 18.5 kg/m^2) and obese (BMI ≥ 30 kg/m^2) women who underwent intracytoplasmic sperm injection (ICSI) in the KrakOvi Clinic in Kraków (Poland) between 2021 and 2024. The control group consisted of patients of normal weight. In order to exclude the influence of age on the results of IVF, patients in all groups were <38 years old patients with PCOS and endometriosis were excluded from the study.

Couples with severe male factor infertility were also excluded. The research was carried out in accordance with the guidelines of the local bioethics committee.

Clinical protocols

Patients were treated using either the long agonist protocol or short antagonist protocol. The type of protocol used depended on the level of AMH and the overall risk of hyperstimulation.

Long agonist protocol

Starting 1 week before the expected menses (cycle day 18–23), patients received the GnRH agonist, triptorelin (Decapeptyl, Ferring Pharmaceuticals, 1 mg/d, sc). After successful pituitary downregulation (when the serum estradiol [E_2] levels were < 40 pg/mL), ovarian stimulation was begun with a fixed daily dose of 150–300 IU recombinant follitropin alfa (rFSH, sc) with or without an additional 75–150 IU menotropin (hMG).

Antagonist protocol

A GnRH antagonist Cetrorelix (Cetrotide, Merck Europe, 0.25 mg/d, sc or Ganirelix Gedeon Richter, 0.25 mg/d), was administered, commencing when the largest follicle reached a diameter of 14 mm. rFSH/hMG was initiated on day 2–4 of the cycle.

The agonist and antagonist protocols were continued up to and including the day of human chorionic gonadotropin (hCG) administration, which was when the leading follicle reached a diameter of 18 mm or more and at least three follicles reached a diameter of 17 mm or more. rFSH was then stopped, and a single sc bolus of 10,000 IU hCG (Eutrig, Samarth Life Sciences) or 6,500 IU rhCG (Ovitrelle, Merck) was administered 36h before the planned time of oocyte retrieval. When there was a risk of OHSS in an antagonist cycle, the trigger was a single sc bolus of triptorelin 2mg, and a freeze-all policy was applied. All follicles 12 mm or larger were aspirated.

Ovarian stimulation monitoring in ICSI

Baseline blood sampling and transvaginal sonography (TVS) were performed on day 2 or 3 of the treatment cycle for all patients. Monitoring of response during the treatment cycle consisted of TVS and blood sampling for hormonal analysis on cycle days: 2–3 (E_2, FSH, LH); 5–6 (E_2); 8–9 (E_2); and day of hCG administration (E_2, P_4). Additional TVS monitoring was performed as clinically indicated.

Frozen embryo transfer (FET)

Treatment with oral E_2 was started on the first, second or third day of the cycle to prime the endometrium and suppress spontaneous follicle growth. Oral estradiol was administered in an incremental fashion 2 mg/day during days 1–7, 4 mg/day during days 8–12 and 6 mg/day from day 13 until embryo transfer. Usually, after 12–14 days of E_2 administration, a vaginal ultrasound examination was performed to measure the endometrial thickness and to confirm the absence of a leading follicle. When the endometrial thickness was >7 mm, P_4 supplementation was commenced, and timing of FET was scheduled accordingly. For t-NC, TVS was performed on day 2 or 3 of menses to rule out any cyst or corpus luteum remaining from the previous cycle. Cycles were usually cancelled when serum P_4 exceeded 1.5 ng/ml on day 2 or 3 of menses. Transvaginal ultrasonographic monitoring was usually started on day 8–10, while endocrine parameters were monitored and serum E_2, LH and P_4 was measured when the leading follicle attained a mean diameter of approximately 15 mm in diameter. Following frequent endocrine and ultrasonographic monitoring, on alternate days or daily, the day of ovulation was precisely documented to schedule the timing of FET.

Clinical pregnancy was defined by the ultrasound confirmation of an intrauterine gestational sac after 8 weeks of gestation with visible foetal cardiac activity. Ongoing pregnancy was defined after over 12 weeks of gestation with visible foetal cardiac activity.

Laboratory protocols

Oocyte-cumulus complexes (COCs) were identified using a stereoscopic microscope and then washed, and after 3h of incubation (approx. 3h) the cumulus cells were removed using hyaluronidase (Gynemed, Germany) and mechanical pipetting. Only oocytes at metaphase II with a first polar body were used for further procedures. ICSI was performed following the standard technique. Embryos were cultured in SAGE® medium (Origio,

Denmark) under an atmosphere of 6.0% CO_2, 5.0% O_2 and balance nitrogen at 37°C. Embryo development was assessed every day. Blastocysts were graded according to the Gardner scoring criteria [8]. Fresh embryo transfer was carried out on day 3 or 5. Blastocysts were vitrified using Kitazato® media and the Cryotop device (Kitazato, Japan) according to the manufacturer's protocol. For FET, blastocysts were warmed in Kitazato media for a minimum of 1.5h before transfer and then placed in EmbryoGlue® medium (Vitrolife, Sweden) medium. The embryo glue was used for all embryo transfers (ET, FET).

Statistical analysis

Non-parametric data, such as differences in the percentage values between groups, were assessed using the chi-squared test. Parametric data were expressed as means ± SD and compared using two-way ANOVA. Differences were considered significant when the P-value was ≤0.05. The statistical analysis was performed using PQStat 1.6.2 (PQStat Soft, Poznan, Poland).

Results

Table 1 presents the results of IVF in underweight, normal weight and obese patients. Underweight patients were the youngest compared to the age of normal weight and obese women (30.2±3 vs. 33.1±3, 32.5±4). Significantly fewer oocytes were obtained from obese patients compared to normal weight patients (8.4±2 vs. 11.3±3). Furthermore, the lowest number of mature oocytes at the met II stage was obtained from these patients. The next lowest indicator in obese patients was the number of blastocysts in comparison to underweight and normal weight patients (2.8±0.2 vs. 3.7±0.4[a], 4±0.3). Moreover, these blastocysts were of worse morphological quality than in the other groups (Fig. 1). In obese patients, 17% of cycles were cancelled due to a lack of oocytes or embryos for transfer. In patients of normal weight and underweight ones, the percentage of cycles cancelled was at a similar level (6% vs. 8.5%).

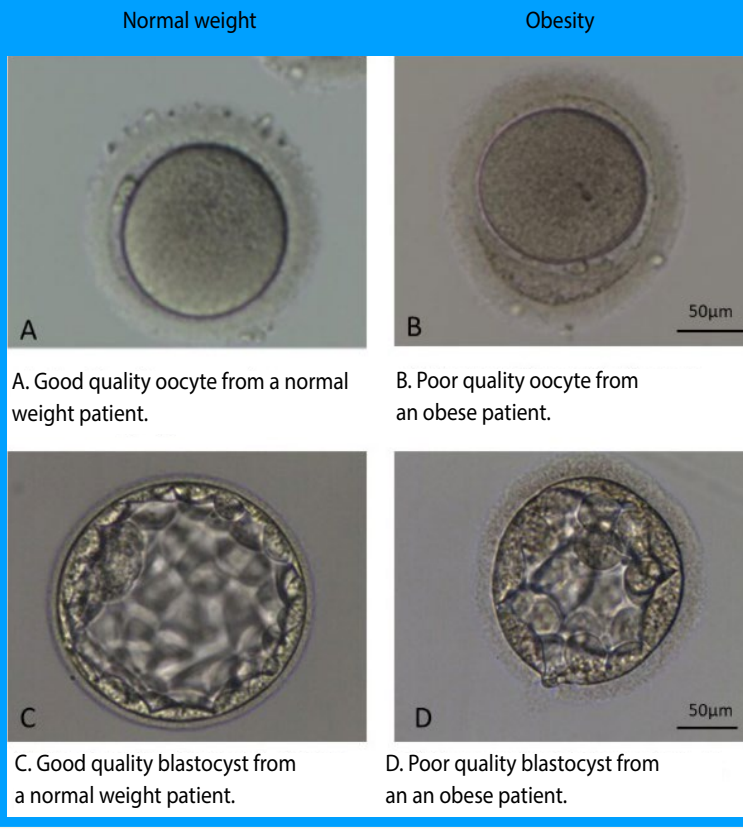
The most commonly used embryo transfer strategy in all groups was FET, but in obese women FET accounted for as many as 75% of all transfers. There was no difference in the implantation rate in underweight patients compared to normal weight (47% vs. 51%), but a lower implantation rate was noted in obese patients (38%).

Table 1. Results of in vitro fertilization depending on the patient's body weight

		Underweight	Normal weight	Obesity
No. of patients (cycle), *n*		35	35	35
BMI (range), mean±SD		(16.9–18.3) 17.9±0.6	(19–24) 22.3±1	(31–41) 35.8±3
Age (years), range, mean±SD		(28–35) 30.2±3	(28–37) 33.1±3	(28–37) 32.5±4
AMH (ng/ml), mean±SD		2.8±0.8	3.4±0.9	3.3±0.7
Oocytes recovery, *n* mean±SD		322 9.2±2	395 11.3±3[a]	294 8.4±2[b]
Ovarian stimulation protocol	Antagonist protocol *n* (%)	25/23 (72%)[a]	31/35 (89%)[b]	27/35 (78%)[a]
	Long agonist protocol *n* (%)	10/35 (28%)[a]	4/35 (11%)[b]	8/35 (22%)[a]
Oocytes at metaphase II stage, *n* mean±SD		248 7.1±1	353 10.1±2[a]	206 5.9±1[b]
Blastocyst, *n* mean±SD		129 3.7±0.4[a]	140 4.0±0.3[a]	98 2.8±0.2[b]
Blastocyst quality	No. of excellent quality *n* (%)	39/129 (30%)[a]	46/140 (33%)[a]	19 (19%)[b]
	No. of good quality *n* (%)	45/129 (35%)[a]	39/140 (28%)[a]	21 (21%)[b]
	No. of medium quality *n* (%)	45/129 (35%)[a]	55/140 (39%)[a]	58 (59%)[b]
Cycle cancelled due to lack of oocytes or blastocysts		3/35 (8.5%)[a]	2/35 (6%)[a]	6/35 (17%)[b]
Embryo transfer	Day 3	3/16 (19%)	3/17 (18%)	2/12 (17%)
	Day 5	2/16 (12%)[a]	4/17 (23%)[b]	1/12 (8%)[a]
	FET	11/16 (69%)	10/17 (59%)[a]	9/12 (75%)[b]
Total implantation rate		16/32 (50%)[a]	17/33 (51%)[a]	12/29 (41%)[b]
Ongoing pregnancy *n* (%)		15/32 (47%)[a]	17/33 (51%)[a]	11/29 (38%)[b]

BMI – the body-mass index is the weight in kilograms divided by the square of the height in metres; AMH – Anti-Mullerian hormone, excellent quality (Bl 4AA, Bl 5AA), good quality (Bl 4AB, 4BA, 5AB, 5BA), medium quality (Bl 4BB, Bl 5BB); FET– frozen embryo transfer; a:b – values with different superscripts within the same rows differ significantly ($p < 0.05$)

Figure 1. The effect of obesity on oocyte and embryo morphology



A. Good quality oocyte from a normal weight patient.

B. Poor quality oocyte from an obese patient.

C. Good quality blastocyst from a normal weight patient.

D. Poor quality blastocyst from an an obese patient.

Discussion

ESHRE (European Society of Human Reproduction and Embryology) and other health organizations generally recommend that women with obesity aiming for IVF/ICSI should be encouraged to lose weight before starting treatment [1,9,10]. ESHRE does not mandate a specific BMI cut-off for accessing treatment, but some fertility clinics consider BMI when assessing a patient's suitability for IVF/ICSI. A common threshold is a BMI between 19 and 30 [10]. However, a significant number of these patients are looking for a quick solution and a "shortcut", especially if they are under the pressure of reproductive aging. Therefore, these patients often decide to undergo the IVF procedure. There are also obese or underweight patients for whom IVF is the only chance to have a child due to, for example, blocked fallopian tubes or the partner's sperm being of poor quality. Our observations and

reports of other authors clearly show that obese patients cannot rely on the same effectiveness of IVF as patients of normal weight [11,12]. However, it seems that underweight patients, for whom most stages of the in vitro procedure are as effective as in patients of normal weight, are in a much better situation.

In obese patients, almost twice as many cycles are cancelled due to the lack of oocytes at metaphase II stage or embryos for embryo transfer compared to patients with normal weight or who are underweight. It can be assumed that the lack of embryos is due to the poor morphological quality of the oocytes. Oocytes collected from obese women are characterized by increased expression of transcripts associated with oxidative stress and lower activity of fat metabolism genes [13]. The formation of free radicals (ROS) damages mitochondria, which limits the maturation of oocytes, which are smaller in obese women and have a thinner *zona pellucida* compared to the oocytes of normal weight women [14]. Poor quality of oocytes and metabolic disorders lead to the arrest of embryonic development [15]. In our study, we also confirmed a significantly lower number of embryos at the blastocyst stage in obese women compared to both normal weight and obese women. Moreover, the blastocysts obtained were characterized by poorer morphological quality, which is probably the result of fertilization with poor quality oocytes. Metabolic and endocrine disorders that accompany obesity negatively affect uterine receptivity and embryo implantation. In our study, the implantation rate in obese women was 10% lower than in women with normal weight and who were underweight.

The main limitation of our research is the small size of the groups studied. The small size of the groups make it impossible to reliably analyze the impact of different stimulation protocols within the group. Another limitation is that the analysis of the results was limited to a comparison of the ongoing pregnancies rates rather than live birth rates. The advantage of our research is that it was conducted at a single centre using a single set of protocols, which ensured the repeatability of the procedures.

Conclusions

To sum up, obese patients undergoing IVF must be made aware that obesity also affects the outcome of this procedure. However, the success of IVF is only the first step towards the birth of a healthy child, and obesity leads to endometrial disorders and also increases the rate of pregnancy complications and miscarriages [16]. If these patients are young, and are not under the pressure of reproductive aging they should definitely consider losing weight before starting the IVF procedure.

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CASE REPORT

The twin reversed arterial perfusion syndrome (TRAP sequence)

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Abstract

Background: The twin reversed arterial perfusion syndrome (TRAP sequence) is a rare congenital sequence and a serious complication of monochorionic multiple pregnancies. The frequency of this sequence is estimated at 1:35,000 pregnancies and 1% of monochorionic pregnancies. In this sequence, one fetus is described as a "semi-donor" or "twin-pumping" (autosite), and the second as a twin acardiac (acardiac twin). The cause is considered to be arteriovenous anastomoses in the placenta, which lead to blood transfusion between the twins.
Material and methods: In this article, we report a case of monochorionic monoamniotic pregnancy resulting from natural fertilization, complicated by TRAP sequence.
Results: The patient gave birth by cesarean section at 34 weeks' gestation to a neonate weighing 2350 g, length 43 cm, with an Apgar score of 8/10.
Conclusions: The outcome of a course of maternity care and possible treatment options in the event of TRAP sequence, as reviewed in the literature, are presented in the article.
Keywords: monochorionic pregnancy complications, Twin reversed arterial perfusion (TRAP sequence)

Introduction

Reversed arterial perfusion sequence (TRAP), also known as twin reversed arterial perfusion sequence (TRAP), is a rare congenital anomaly that constitutes a serious complication of multiple monochorionic pregnancies. Its incidence is estimated at one in 35,000 pregnancies and 1% of monochorionic pregnancies [1]. In this syndrome, one foetus is referred to as the "donor twin" or "pumping twin" (autosite), while the other is

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referred to as the acardiac twin. The cause of this sequence is believed to be arteriovenous anastomoses within the chorionic plate. This abnormal vascularization of the shared placenta leads to blood transfusion between the twins. Deoxygenated blood flows through the umbilical artery of the anaemic twin and returns through the umbilical vein, leading to underdevelopment of the upper body parts of this twin [2]. In this situation, the donor twin is forced to supply blood to the other foetus through the collateral arterial circulation of the shared placenta. This may result in the development of congestive heart failure in the pumping twin. The presence of the sequence increases the risk of preterm birth due to increasing polyhydramnios or iatrogenic factors. Given the estimated mortality rate of acardiac twins, the goal of obstetric care is to save the donor twin by isolating their circulatory systems. This is achieved by caesarean delivery [3], endoscopic vascular ligation [4], intravascular insertion of a metal coil [5], ultrasound-guided chemical embolization [6,7] (e.g., with 100% ethanol), or laser obliteration [8].

Case Report

A 30-year-old patient in her first pregnancy, 22 weeks pregnant, with RhD serological incompatibility, was scheduled for a consultation and further diagnostic evaluation at the Clinic of Gynaecological Endocrinology at the University Hospital in Krakow. Previous ultrasound examinations at another centre had reported abnormal findings. At 13+3 weeks of gestation, the patient underwent a first-trimester genetic ultrasound using a GE Voluson 730 Expert system with a 4-8 L RAB transducer. An acardiac foetus was suspected.

From the interview it emerged that the patient had conceived naturally after four or five months of trying. Four months before conception, she began taking folic acid 0.4 mg/day and took iodine for the first three months of pregnancy. The patient had a seven-day viral infection during which she did not receive pharmacotherapy.

At 23+0 weeks of gestation, a follow-up ultrasound was performed, and the diagnosis of an acardiac foetus was confirmed (twin A: CRL – 78.6 mm, BPD = 57.3 mm, HC = 211 mm, OFD – 73.3 mm, AC – 185 mm, FL – 38.7 mm; twin B: FL = 38.4 mm).

At 24+0 weeks of gestation, the patient underwent an MRI (Table 1). At 26+2 weeks of gestation, the patient was readmitted to the Clinic due to threatened preterm labor caused by a urinary tract infection. Antibiotic therapy improved her general condition and resolved her dysuria. Steroid therapy was then administered. The patient was discharged home in good

general condition, with a viable pregnancy. Her due date was scheduled for May 8, 2012, according to Naegele.

Table 1. MRI report from 18.01.2012

The examination was performed using SSET2, FSPGRT1fs, DWI, and 2DFIESTA sequences in the coronal, transverse, and sagittal planes, with slice thicknesses of 4 mm, 5 mm, and 8 mm.
Pregnancy I, 24 weeks.
Twin pregnancy. The placenta was located on the posterior wall, with discreetly higher signal levels visible in the central part – lobular oedema? No cystic lesions or haemorrhages were detected. The amount of amniotic fluid was normal.
Fetus A: alive, male, in a breech presentation. Eyeballs and facial structures were properly developed. The skull was normal and symmetrically arched. Brain structures were developed appropriately for the foetus's age – the neural tissue layer thickness and signal were normal, the ventricular system was not dilated and without displacement. The cerebellum and pons were normal. The spinal canal was of normal width, symmetrical, and without signs of clefting. A single spinal cord was visible within the canal. The nuchal cistern was of normal width. The heart and lungs were normal. The liver, spleen, stomach, small intestines, large intestine, kidneys, and urinary bladder were normally developed. The foetal limbs were normally developed. The feet and hands were normal.
Fetus B: most likely male, with a narrow, single-vessel umbilical pedicle, lower limbs, and pelvis (dystrophic bony structures) visible, with significant subcutaneous tissue oedema (16.7 mm thick). The remaining organs of the second foetus were missing.
No septum/membrane was detected separating foetuses A and B, suggesting a monoamniotic pregnancy.
The image is consistent with reverse arterial perfusion syndrome of the acardius amorphous type, and no neural tissue was detected, ruling out acardius myelacephalus.

On March 28, 2012, at 34+0 weeks'gestation, the patient was readmitted to the Clinic due to amniotic fluid leakage. An ultrasound was performed to assess the pregnancy (Figs. 1 and 2), and a CTG was obtained (Fig. 3).

The pregnancy was terminated by caesarean section using the Misgav-Ladach procedure. She delivered a live son weighing 2350 g and measuring 43 cm in length, with an Apgar score of 8/10 cm, and a stillborn foetus weighing 98 g and measuring 12 cm in length (Figs. 4 and 5).

An extensive general and neurological examination of the newborn revealed no abnormalities. The newborn was septic, and given the significant obstetric history, empirical antibiotic therapy was prescribed and continued for nine days.

Blood and urine cultures were negative. During hospitalization, the newborn had good circulation, and basic vital signs were normal. From birth, the newborn was enterally fed his mother's milk with the addition of a preterm formula. The newborn gained weight normally. On the second day, he was vaccinated against hepatitis B and BCG. Due to RhD incompatibility (mother: blood group B, RhD negative; father: RhD positive), a qualifying test for administration of anti-D immunoglobulin was performed. No anti-D antibodies were detected in the test; therefore, the patient was qualified for administration of 300 mg of anti-D immunoglobulin the day after caesarean section. Due to an uncomplicated postpartum period, the patient was discharged home in good general and local health on the fourth day after delivery.

Figure 1. TA ultrasound result – pregnancy 34 +0 weeks. – pregnancy 34 +0 weeks

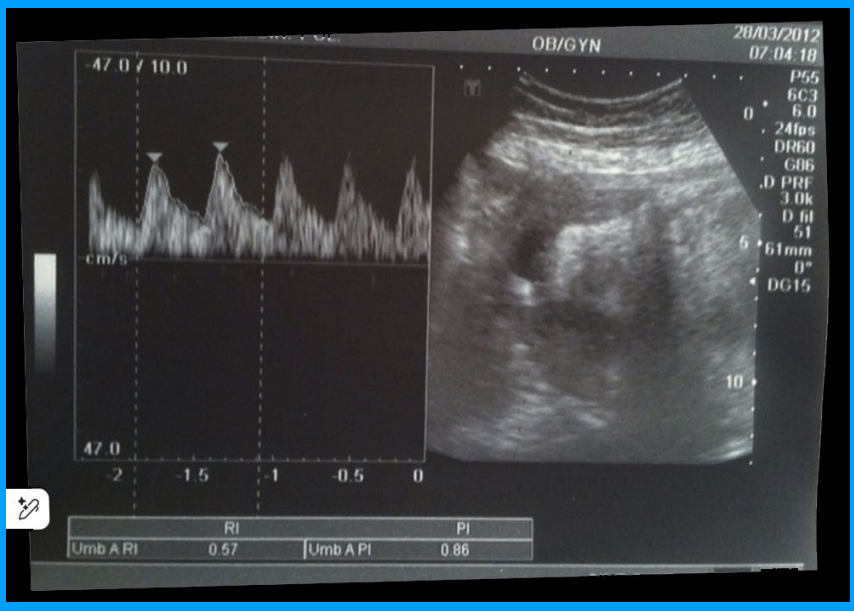


Figure 2. Ultrasound result – pregnancy 34 +0 weeks

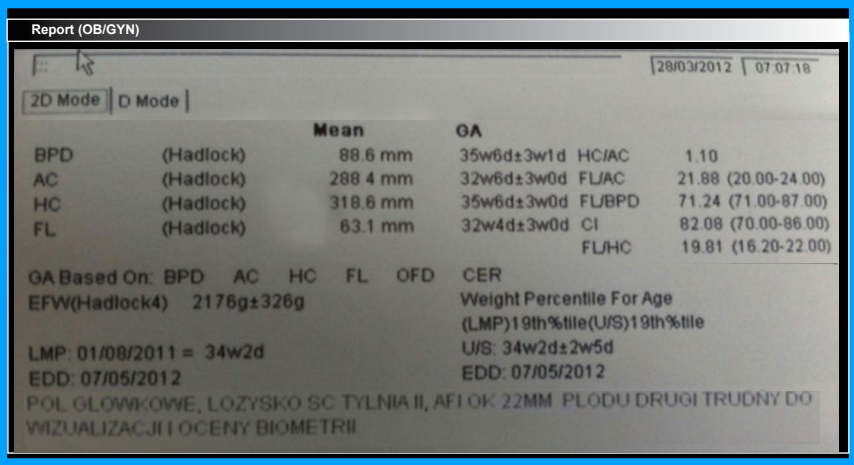


Figure 3. Recording CTG – pregnancy 34+0 weeks

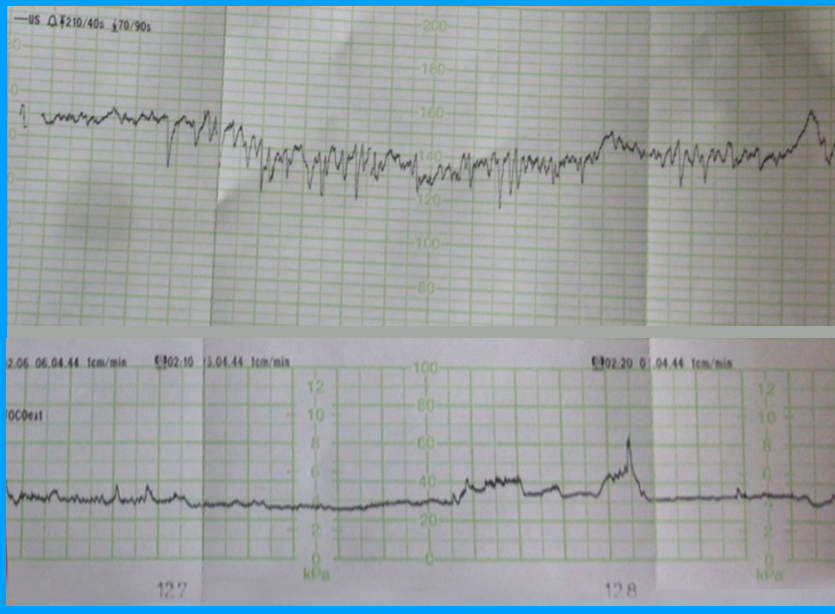
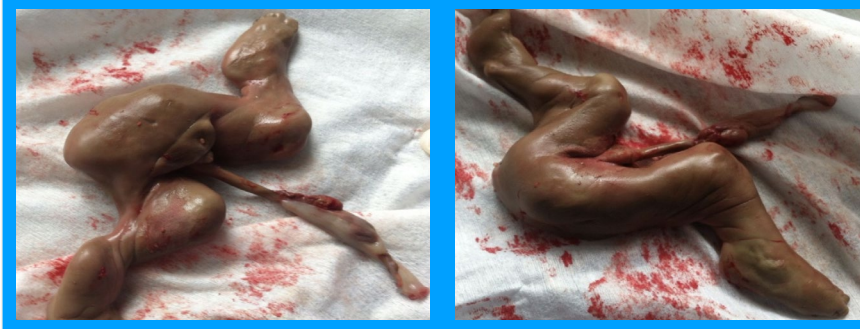


Figure 4,5. Twin B after birth



Discussion

The goal of obstetric care in pregnancies complicated by TRAP sequence is to save the donor twin by separating the circulatory systems of both twins – stopping blood flow in the abnormal twin. Of the many available methods, such as endoscopic vascular ligation, laser obliteration, and less commonly used techniques such as intravascular metal coil insertion or ultrasound-guided chemical embolization, we chose caesarean delivery. The patient was under the Clinic's constant care throughout the pregnancy. The choice of treatment in this case was based primarily on the good general condition of twin A and the absence of a heartbeat in the twin considered acardiac. In our case, the absence of any signs of foetal damage in twin A was considered unusual. The literature describes abnormalities in the donor twin, such as generalized hydrops fetalis, intrauterine growth restriction (IUGR), soft tissue oedema, pleural effusion, hepatosplenomegaly, and myocardial damage leading to foetal death, severe heart failure, pericardial effusion, or tricuspid valve regurgitation [9,10].

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CASE REPORT

Chronic adrenal insufficiency (Addison's disease) – diagnostic obstacles, problems of the patient and his or her family

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Abstract

Addison's disease (AD) is a relatively uncommon illness presented by decreased adrenal production of adrenocortical hormones - mainly glucocorticoids. We present a case of a patient who had symptoms of chronic fatigue, depression that made it difficult for her to carry out everyday household activities. In basic laboratory tests, they mainly noted low sodium (Na), increased potassium (K) and low fasting glucose concentration. The patient's informed consent was obtained for the presentation of anonymised laboratory, clinical and imaging data. On the basis of the clinical picture and hormonal tests, Addison's disease was confirmed. Significant clinical improvement was observed following the addition of hydrocortisone to the treatment regimen. Advances in optimizing treatment for patients with Addison's disease have enabled them to lead normal lives. However, it is important to continuously educate patients and healthcare professionals about the ever-present threat of adrenal crisis.

Keywords: Addison's disease, primary adrenal insufficiency, hyperkalemia, hyponatremia, adrenal crisis

Introduction

Addison's disease (AD) was first described in 1855 by Thomas Addison as a syndrome characterized by wasting and hyperpigmentation occurring with adrenal damage [1]. However, it was not until 1949 that Edward Calvin Kendall developed a method to synthesize cortisone, a therapeutic breakthrough in the treatment of the disorder. Nowadays, this relatively rare disease, an uncontrolled course of which threatens the life of the patient, still causes many challenges. AD is a syndrome of clinical symptoms caused by primary adrenal insufficiency resulting in a deficiency of adrenal cortex hormones, particularly cortisol. The most common cause of the

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disease is autoimmune-mediated atrophy of the adrenal cortex due to the presence of anti-adrenal antibodies (often with coexisting autoimmunity to thyroid cells), and less commonly adrenal tuberculosis and other infectious diseases, destruction of the adrenal cortex by tumours or tumour metastases, amyloidosis, a condition after adrenal haemorrhage, bilateral adrenalectomy or drug-induced inhibition of glucocorticosteroid synthesis [2]. AD is manifested by nonspecific symptoms. The main symptoms are hyponatremia and hyperkalaemia in laboratory tests, a tendency towards hypoglycaemia (especially post-workout), low blood pressure, and characteristic darkening of the skin [3]. The main complaint reported by patients is excessive fatigue, even with low-level exertion, constant weakness and periodic fainting with orthostatic etiopathogenesis, weight loss, lack of appetite, salt craving, loose stools, muscle and joint pain [4,5]. The symptoms may initially resemble depression. Hormonal tests show low cortisol values and high levels of adrenocorticotropic hormone (ACTH) resulting from the lack of inhibition by cortisol (negative cortisol feedback mechanism on the pituitary gland and hypothalamus) [2]. To determine the secretory reserve of the adrenal cortex, a test with a synthetic derivative ACTH (Synacthen) is used.

Treatment of the disease consists in supplementing the missing hormones, primarily hydrocortisone.

Case presentation

For several years a 40-year-old female, the mother of three children, had experienced chronic fatigue, lethargy, extreme drowsiness and palpitations on slight exertion, e.g. when making breakfast for the children. She was tearful, had problems with climbing up to the first floor caused by significant fatigue, she had hyperpigmentation of the skin with reduced prominence of the hand creases (figures no. 1 and 2), light sensitivity, skin that burnt easily due to exposure to sunlight, and repeated convulsions lasting a few minutes. The symptoms worsened after the birth of her third child (five years ago). In addition, she experienced weight loss (more than 10 kg in six months), pain in the lower limbs after exertion, memory and concentration difficulties, attention problems, depression, anxiety, insomnia, and an excessive desire to eat salty food; the family reported that food prepared by her was oversalted. The patient was negatively perceived by the family and community due to her lack of strength to do any work at home. The patient felt an improvement in her well-being after drinking electrolyte preparations.

Figure 1. Author's own photographs – comparison of the hand of a patient with Addison's disease with the hand of a doctor – note the dark complexion of the patient's skin

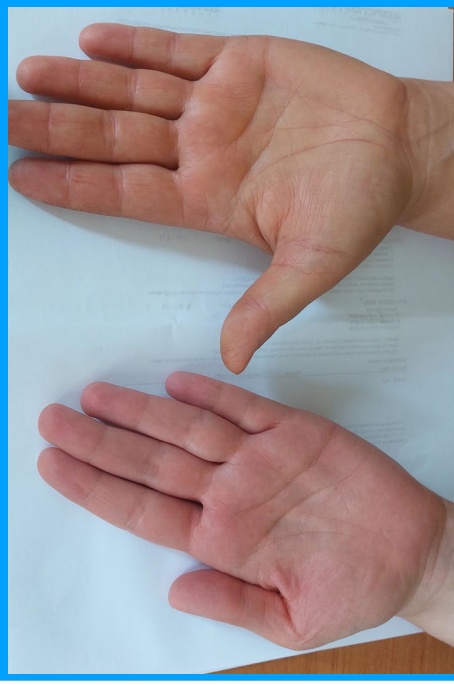

Figure 2. Author's own photographs – comparison of the hand of a patient with Addison's disease with the hand of a doctor – note the dark complexion of the patient's skin

In the physical examination, the following symptoms were noteworthy: hyperpigmentation of the skin, less prominent finger lines and creases on the hands, dimming of the nipples, low blood pressure of 90/60 mmHg, and a heart rate of 70 per minute.

After the birth of her third child, the patient experienced symptoms of very high fatigue and depression. A baseline blood count was ordered, but the results showed no abnormalities. Repeatedly low blood sodium and elevated potassium concentrations were also present in laboratory tests. The patient began to report multiple depressive disorders, balance problems, anxiety, memory and concentration difficulties. She was referred by a general practitioner to a psychiatrist, who prescribed multiple antidepressants. Treatment with antidepressants did not bring clinical improvement.

She was admitted to the Hospital Emergency Department in July 2018 due to dyspnoea occurring with very slight exertion, and limited tolerance to any exertion. Laboratory tests were notable for hyponatremia (Table 1).

Table 1. Laboratory tests after admission to Emergency Department in 2018

Laboratory tests (reference range)	Laboratory results
Na (136–145 mmol/l)	129.0 mmol/l
K (3.5–5.1 mmol/l)	4.84 mmol/l
Cl (98–107 mmol/l)	98.0 mmol/l
Ca (2.15–2.50 mmol/l)	2.51 mmol/l
CRP (0–5 mg/l)	<1.0 mg/l
GFR (>60 ml/min/1.73m^2)	70.0 ml/min/1.73m^2
Creatinine (0.50–0.90 mg/dl)	0.94 mg/dl
Glucose (70.0–99.0 mg/dl)	112 mg/dl
D-Dimers (0–499 ng/ml)	254 ng/ml

Legend: Na – sodium; K – potassium; Cl – chloride; Ca – calcium; CRP – C-reactive proteine; GFR – glomerular filtration rate.

In 2018 and 2019, there were two more hospitalizations due to a sudden deterioration in health status. The laboratory tests are shown in Table 2.

Table 2. Laboratory tests after admission to Hospital in 2019

Laboratory tests (reference range)	Laboratory results
Na (136–145 mmol/l)	137.0 mmol/l
K (3.50–5.10 mmol/l)	5.12 mmol/l
Ca (2.15–2.50 mmol/l)	2.35 mmol/l
Fe (5.83–34.50 mmol/l)	2.92 mmol/l
Glucose (3.9–5.5 mmol/l)	3,75 mmol/l
Thyroid hormonal tests	TSH – 7.49 uIU/ml (ref. range: 0.27–4.2) fT4 – 15.42 pmol/l (ref. range: 12.0–22.0) fT3 – 4.48 pmol/l (ref. range: 3.1–6.8) anti TPO – 546.0 IU/ml (ref. range <34) anti TG – 98.0 IU/ml (ref. range <115).
Cortisol (2.3–19.4 µg/dl)	at 8 a.m. 1.02 µg/dl
Diurnal cortisol profile	at 6 a.m. cortisol – 0.88 ug/dl at 8 a.m. cortisol – 0.52 ug/dl at 12 a.m. cortisol – 1.45 ug/dl
ACTH (7.2–63.0 pg/ml)	> 2000.0 pg/ml
DHEAS (60–337ug/dl)	5.76 µg/dl
Anti-adrenal antibodies	positive ++

Legend: ACTH – adrenocorticotropic hormone; DHEAS – dehydroepiandrosterone sulphate; TSH – thyroid-stimulating hormone; fT4 – thyroxine; fT3 – triiodothyronine; Anti-TPO – Antithyroid peroxidase antibodies; Anti-TG – thyroglobulin antibodies; Fe – ferrous.

The patient received the following treatment: hydrocortisone (pills) at a dose of 10–10–0 mg/day; fludrocortisone at a dose of 0.1 mg – ½ pill/day in the morning; prasterone in pills at a dose of 10 mg/day. Then L-thyroxine treatment was added, which resulted in improved well-being, complete resolution of excessive fatigue, lethargy, brightening of the skin, no seizures, no memory impairment, no dizziness, and resolution of depression and anxiety. The psychiatrist decided to discontinue all antidepressants and anti-anxiety medication. The patient reported no psychiatric symptoms. There was a significant improvement in blood pressure, which was oscillating around the reference range of 120/80 mmHg. Currently the patient is feeling very well and has stopped fainting. Blood laboratory tests

after treatment revealed an improvement in the sodium level in the serum and increased levels of glucose.

An abdominal CT scan performed in 2019 showed small narrow adrenal glands without focal changes. Thyroid ultrasonography revealed inhomogeneous and decreased echogenicity. The thyroid volume was 7.7 ml (left lobe 2.6 ml; right lobe 5.1 ml). The patient was trained to increase the dose of hydrocortisone in special situations, i.e. in the case of fever, illness, vomiting, nausea, minor and major procedures. The patient's family was also trained on how to manage this disease.

Discussion

This case represented non-specific initial symptoms, which included chronic excessive fatigue and fainting. The patient was treated psychiatrically due to the significant presence of negative symptoms. The ineffectiveness of the diagnosis contributed to the lack of improvement in health status and only attempted to alleviate psychiatric symptoms. Over time, some symptoms became more acute, and hospitalization in emergency departments was necessary. The case teaches us that when a patient complains of chronic fatigue and excessive fatigue despite little effort, chronic adrenal insufficiency should also be considered in a differential diagnosis. It is necessary to determine the concentrations of electrolytes (Na, K) and glucose, the concentrations of which may suggest the development of the disease. Clinical assessment of the patient (low blood pressure, darkening of the skin, hypersensitivity to the sun) is important. Establishing the cortisol and ACTH concentrations allows AD to be diagnosed. Elevated ACTH was caused by the lack of inhibition due to insufficient cortisol concentrations (the pituitary-adrenal axis is regulated according to negative feedback) [6–8]. The lack of cortisol was the cause of hyponatremia and hyperkalaemia. Undiagnosed or inadequately treated AD leads to the risk of the development of an adrenal crisis, which is a directly life-threatening condition. The main symptoms are severe weakness, impaired consciousness, vomiting, loose stools, low blood pressure accompanied by tachycardia and shock. Treatment consists of the rapid administration of hydrocortisone: 100 mg iv as a bolus, followed by a 100 mg iv infusion every six hours and the supply of fluids and glucose [9]. Patients diagnosed with AD should be informed about the risk of adrenal crisis and its prevention. According to a multicentre study conducted in the UK, Canada, Australia, and New Zealand, about 8% of patients diagnosed with adrenal insufficiency are hospitalized for adrenal crisis annually [10]. It is necessary to educate patients about the need to increase the dose of hydrocortisone in the event of diseases that, according

to retrospective studies, contribute the most to the occurrence of adrenal crisis (gastroenteritis (35–45%) and fever (17–24%), trauma, surgery, dental procedures and situations of severe mental stress) [6,11]. A doctor noticing a low concentration of sodium, a high concentration of potassium and a low concentration of fasting glucose in a patient with symptoms of chronic fatigue should pay particular attention to skin pigmentation and low blood pressure values and, suspecting AD, should refer the patient to an endocrinologist for an appropriate diagnosis. When diagnosed, it is necessary instruct the patient and his or her family about the procedure in the case of fainting, sport activity and the "sick days" rules.

Conclusions

Advances in optimizing treatment for patients with Addison's disease have enabled them to lead normal lives. However, it is important to continuously educate patients and healthcare professionals about the ever-present threat of adrenal crisis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

The patient's informed written consent to publish the data was obtained.

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REVIEW PAPER / META-ANALYSIS

Prehabilitation before total knee arthroplasty (TKA): A literature review and proposed methods for increasing its effectiveness

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Abstract

Prehabilitation, understood as a targeted physiotherapeutic and educational intervention conducted before total knee arthroplasty (TKA), is becoming increasingly popular as a method of improving postoperative outcomes. The aim of this study is to analyze contemporary research on the effectiveness of prehabilitation in patients preparing for TKA, with particular focus on physical function, pain, and length of hospital stay, as well as to explore ways to enhance the effectiveness of prehabilitation programmes. The review includes one experimental study and one systematic review, covering a total of over 1,600 patients. The results suggest that prehabilitation programmes may shorten the hospital stay and reduce preoperative pain, whereas their effect on long-term function and muscle strength remains less clear. Further research is needed to optimize prehabilitation programmes and definitively determine their efficacy.
Keywords: total knee arthroplasty, neuromuscular electrical stimulation, prehabilitation, blood flow restriction training, motor imagery

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed orthopaedic procedures. Many patients experience muscle weakness, a reduced range of motion (ROM), and pain prior to surgery, which can prolong the recovery and return to functional activities. Prehabilitation aims to prepare patients through strengthening exercises, improvement of endurance and muscle flexibility, and health education. The goal is to shorten the hospital stay, improve physical function, and enhance patient comfort following TKA. Additionally, this study aims to identify and discuss methods that could potentially increase the effectiveness of prehabilitation programmes.

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Methods

Two main sources were analyzed: a randomized clinical trial [1] and a systematic review of 22 randomized controlled trials (RCTs) involving patients preparing for TKA [2]. Characteristics of participants, types of prehabilitation programmes, duration of interventions, and outcomes related to function, pain, ROM, and length of hospital stay (LOS) were evaluated.

Results

Prehabilitation Programmes

Studies employed multimodal interventions.

Strength exercises: knee extensions, bridges, squats, leg press; goal: to increase lower limb muscle strength.

Aerobic training: treadmill walking, stationary cycling, stepper; goal: to improve cardiovascular endurance.

ROM and flexibility exercises: heel slides, AROM, PROM, stretching of hip flexors and calves; goal: to maintain a ROM and prevent contractures.

Balance and motor control training: single-leg stance (SLS), weight shifting, multi-directional walking; goal: to improve neuromuscular control.

Patient education and supportive techniques: HEP, neuromuscular electrical stimulation (NMES), massage, mobilization, heat/cold therapy; goal: to reduce preoperative pain and stress.

Study Characteristics

Experimental study [1]: 45 patients; intervention: prehabilitation + education vs. education only; duration: 4–6 weeks. Results: small, statistically non-significant improvements in function (Chair Stand Test) and KOOS-ADL.

Systematic review [2]: 1,601 patients; home-based or outpatient programmes; duration: 4–12 weeks; compliance ~90%. Results: significant reduction in LOS (MD − 0.43 days), decreased preoperative pain; no significant changes in long-term function and muscle strength.

Proposals to Enhance Prehabilitation Effectiveness

This study evaluates that, to enhance the effect of prehabilitation before TKA, it is reasonable to incorporate NMES in addition to conventional exercises. NMES is a method in which electrical impulses induce muscle contraction, activating both peripheral muscle fibres and central motor pathways. A systematic review and meta-analysis [3] demonstrated that postoperative NMES improves quadriceps strength: standardized mean difference (SMD) was 0.81 at 1 month, 0.55 at 1–2 months, 0.42 at 3–4 months, and 0.46 at 12–13 months after TKA. NMES also showed moderate effects on pain and

function (Timed Up and Go [TUG] test: −2.23 s; 3MWT: +28.35 m). Based on these data, it can be hypothesized that adapting NMES to the preoperative period may also yield positive effects. The present study proposes that high-intensity preoperative NMES could additionally reduce quadriceps atrophy, improve neuromuscular activation, and accelerate post-TKA strength recovery. This effect may be explained by a larger muscle fibre reserve, lower relative functional loss, "motor memory", and enhanced central motor activation, the muscle "wakes up" faster after surgery and recruits motor units more easily.

Furthermore, to increase prehabilitation effectiveness, blood flow restriction training (BFRT) can be considered. BFRT may be particularly effective as a component of prehabilitation before TKA. BFRT involves performing low-load exercises while partially occluding arterial inflow and venous outflow to the targeted limb, creating a localized hypoxic and metabolic stress environment that promotes anabolic signaling pathways responsible for muscle hypertrophy and strength gains at relatively low mechanical loads. According to current evidence specific to knee arthroplasty [4], prehabilitation programmes incorporating BFRT for 4–8 weeks before surgery have demonstrated significant improvements in muscle strength and functional outcomes, with some RCTs reporting greater gains in knee extensor and leg press strength, as well as enhanced early recovery of physical performance when compared to usual care without structured preoperative interventions. Mechanistically, BFRT stimulates metabolic stress and growth factor production (e.g., IGF-1, GH), while also activating vasoactive metabolites and the vascular endothelial growth factor, which may enhance local angiogenesis and increase post-occlusion blood flow, contributing to improved tissue perfusion, muscle adaptation, and functional reserve prior to TKA. These effects are achieved with much lower joint loading than traditional high-intensity resistance training, making BFRT particularly suitable for patients with painful or functionally limited knees who are unable to tolerate heavy mechanical stress during prehabilitation.

Another study demonstrates clinical data on the effectiveness of BFRT in the context of TKA: a 6-week prehabilitation programme with BFRT (cycling exercises, twice weekly, cuff pressure at 40% of individual occlusion limit) was conducted on 30 patients [5]. Post-prehabilitation, quadriceps strength increased by approximately 170% (compared to ~91% in an active control group), and thigh circumference (muscle mass indicator) increased by ~7% ($p < 0.05$). Postoperatively, patients maintained benefits: thigh circumference remained above baseline, and several KOOS domains improved significantly more than controls. Thus, I hypothesize that preoperative BFRT of an appropriate intensity may limit quadriceps atrophy preoperatively,

stimulate neuromuscular activation, increase the muscle fibre reserve and facilitate faster strength recovery after TKA. Although direct mechanistic data (e.g., cellular changes, fibre type, motor activation) for TKA are limited, Erickson's protocol shows that BFRT may influence both strength and muscle morphology, and knee biomechanics. Inclusion of BFRT in prehabilitation could provide additional adaptive stimuli and contribute to better postoperative outcomes.

It can also be considered reasonable to include neurorehabilitation techniques, such as motor imagery (MI) and action observation (AO), in the prehabilitation protocols. These methods rely on mirror neuron activation and are promising complements to TKA prehabilitation. The main goal of MI and AO is to reduce arthrogenic muscle inhibition (AMI), a condition in which the quadriceps "shuts down" after surgery due to pain, swelling, and joint receptor damage, hindering full contractions and slowing functional recovery.

During MI, the patient imagines performing movements, e.g., controlled knee extensions or squats, while AO involves observing correct movement patterns, e.g., via video. These methods activate the motor cortex and central motor pathways, supporting faster muscle activation and improved motor unit recruitment postoperatively. Studies have shown that adding MI to standard TKA rehabilitation may improve quadriceps strength (SMD ≈ 0.88) and reduce pain (SMD ≈ 0.63) [6,7]. This enables patients to regain knee function more quickly, with more effective neuromuscular activation post-surgery.

Alongside this, graded motor imagery (GMI) therapy would be clearly safe and effective for patients awaiting knee arthroplasty surgery. GMI is a staged neurorehabilitation approach consisting of three sequential components: (1) laterality recognition, in which patients cognitively identify left versus right limb images to activate motor planning networks without physical movement; (2) explicit MI, involving first-person mental simulation of functional movements without joint loading; and (3) mirror therapy, which provides visual feedback to reinforce non-threatening movement representations.

Recent evidence suggests that GMI training may produce clinically meaningful effects in orthopaedic rehabilitation, extending beyond pain modulation to functional motor recovery. In a randomized controlled study [8], the addition of structured MI training to conventional physiotherapy resulted in faster recovery of gait performance, reduced pain, and a lower incidence of falls compared with standard rehabilitation alone. Patients who underwent GMI training demonstrated significantly better functional mobility, as assessed by the TUG test, indicating superior integration of motor control

during real-world walking tasks. Importantly, the authors emphasized that "[…] our MI improvement generalized to real walking, with better recovery of motor performance for actual gait, as measured by the TUG test," [8:5] highlighting a clear transfer from imagined to performed movement.

Beyond gait speed and mobility, the GMI group also showed a reduced number of falls and near-falls during follow-up, suggesting improved postural control and safer locomotion. These findings indicate that GMI does not merely influence subjective perception of movement, but actively enhances sensorimotor organization and movement execution. From a prehabilitation perspective, introducing GMI before TKA may therefore be particularly advantageous. Preoperative exposure to GMI could prime central motor representations, reduce maladaptive protective movement strategies, and establish more efficient gait and movement patterns prior to surgery. As a result, patients entering postoperative rehabilitation may demonstrate earlier functional engagement, reduced fear of movement, and faster restoration of walking ability, having already learnt and cognitively integrated the principles of GMI.

While direct evidence for preoperative application is still limited, this transfer of MI-induced improvements to real motor performance supports the hypothesis that prehabilitation-based GMI could contribute to accelerated and safer postoperative recovery following TKA, particularly in terms of gait quality, functional mobility and fall risk reduction. Importantly, GMI is especially suitable for patients awaiting knee arthroplasty because it does not require large-amplitude or loaded movements of the symptomatic joint, thereby minimizing the risk of pain provocation, avoidance behaviours, or reinforcement of maladaptive movement patterns, and allowing effective neural preparation without exacerbating the patient's condition.

In addition to the interventions discussed above, proprioceptive neuromuscular facilitation (PNF) may offer a targeted and safe approach to prehabilitation before TKA. Evidence from RCTs in knee osteoarthritis populations [9] shows that specific PNF techniques, such as rhythmic stabilization, hold-relax, and contract-relax patterns, significantly improve pain, joint ROM, balance, and functional mobility compared to conventional physiotherapy. For instance, rhythmic stabilization, involving isometric co-contractions against manual resistance in multiple directions, enhanced knee joint stability and proprioceptive acuity, leading to improved balance and a reduced risk of falls. Hold-relax and contract-relax stretching applied to the quadriceps and hamstrings increased flexibility and ROM, while simultaneously decreasing protective muscle guarding, which can limit functional movement. Patients demonstrated improvements in functional tests, such as the TUG, SLS, and gait parameters, indicating better neuromuscular control

and movement efficiency during dynamic tasks. These effects are particularly relevant for prehabilitation, as they prime the neuromuscular system, reduce AMI, and optimize movement patterns without imposing high mechanical loads on the arthritic knee. Consequently, integrating PNF into pre-TKA programmes could facilitate safer and more efficient postoperative recovery by preparing patients with improved proprioception, balance, and functional mobility, while minimizing pain and risk of maladaptive movement patterns.

Discussion

The available evidence suggests that prehabilitation before TKA provides measurable benefits in reducing the hospital stay and preoperative pain. The effects on postoperative physical function and muscle strength remain inconclusive. Incorporation of NMES, BFRT, MI, AO, GMI, and PNF could potentially enhance programme effectiveness, particularly with respect to quadriceps strength and neuromuscular activation; importantly, these interventions may also represent a safe and low-pain preoperative strategy, as they allow neuromuscular priming with minimal mechanical load on the affected joint and a low risk of pain provocation or symptom exacerbation. Nevertheless, further clinical research is required to establish optimal protocols.

Conclusions

Prehabilitation may improve patient preparation for TKA by reducing preoperative pain and shortening the hospital stay. Incorporating modern techniques such as NMES, BFRT, GMI, PNF, and AO may further enhance programme effectiveness, especially in terms of muscle strength and function, but additional studies are needed to confirm efficacy and determine optimal training parameters.

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