Methods of Urethral Reconstruction in Metoidioplasty

Doctoral (PhD) Thesis

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2023

1. INTRODUCTION

1.1. TERMINOLOGY

Transgenderism is as old as human civilization itself, and evidence of this can be found in ancient Greece and Rome (1, 2). Its first medical records date from the beginning of the twentieth century, and the word “transsexualism” first appeared in Germany in 1923 – originally coined by Magnus Hirschfeld and Wilhelm Stekel (3-6), it was subsequently popularized worldwide by David Oliver Cauldwell and Harry Benjamin, and John Money (7-10). Later, in 1965, J. Oliven replaced the misleading term “transsexualism” with the more exact “transgenderism” (11-13). Most transgender people reject the use of the term “transsexual”, a fact which has been widely publicized since 1979: “Gender doesn’t have to do with bed partners, it has to do with identity” / “Sexuality is who you sleep with, but gender is who you are” (14, 15).

Transgender people are characterized by the fact that their gender identity, appearance and behaviour do not correlate with their birth (biological) sex, and this does not meet the cultural and social expectations associated with their birth sex (16-18).

This condition may lead to severe gender dysphoria, a sense of discomfort, self-rejection, a drastic deterioration in the quality of life, and social isolation. Transgender people therefore typically develop a strong urge to change, i.e. to transition.

In the narrowest sense, those who are transgender are people whose gender identity is opposite to the sex they were born with: trans women (male-to-female (MtF) transgender) and trans men (female-to-male (FtM) transgender). In a broader sense, however, the term includes further non-binary groups (those who are gender queer, third gender, agender, androgynous, bigender, pangender, gender fluid, and other groups) which cannot be fitted into the binary gender concept of cisnormativity (19-24).

Transgender people do not necessarily aspire to the full social, legal or medical recognition of their gender, so sometimes – in a very broad sense – cross-dressers may also be classified under the term (25).

In the tenth revision of its International Classification of Diseases (ICD-10), the World Health Organization (WHO) introduces the term “gender identity disorders” (F6400). ICD-11 introduces a new term named “gender incongruence in children, adolescents and adults”. At the suggestion of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM)

(26-28), the classification of previous versions underwent numerous revisions in order to avoid stigmatization and depathologize transgenderism.

Since 2010, many have declared that transgender people should have equal rights in both society and healthcare. In the interests of making them feel as comfortable as possible and to avoid provoking hostile behaviour, clinicians are advised to discover and use a patient's preferred pronouns and gender terminology (29).

Transgenderism is a concept independent of sexual orientation (hetero-, homo-, bi-, asexual, etc.), and consequently the term "transsexual" is now considered extremely outdated (30, 31). Some transgender people request medical (psychiatric, hormonal, surgical) help in order to reduce their feelings of gender dysphoria and greatly improve their quality of life (32).

In recent years, the number of transgender people has shown a significant overall increase, transition medicine has developed enormously, trans-health working groups have been established, and, due to the joint efforts of both professionals, transgender people themselves, and other members of the public, the "visibility" of transgender people has become globally wider. The treatment of transgender people requires a multidisciplinary approach and it is frequently a lifelong process. The publication summarizing the most widely used and accepted professional guidelines is the Standard of Care (SOC) published by the World Professional Association of Transgender Health (WPATH). The SOC is currently in its eighth version, and it has been translated into many languages (33). The WPATH is actively engaged in the teaching of new health areas/border areas and in gaining knowledge of and solving a variety of health, legal, ethical, social and other issues.

The process of transition can entail individual, legal, social and health sub-processes. In the majority of cases, these processes are related to one other; one may follow the next, or certain processes may take place simultaneously, but there are also cases where at a given point an individual's severe dysphoria is alleviated and they no longer need to take any further active steps in order to integrate into society and be able to live in harmony with themselves. In the light of this, it can be stated that transition does not consist of obligatory elements, but rather a series of separate events in which the individual, their immediate community and the expert working group (preferably) work together to improve the individual's quality of life. Certain elements of surgical therapies are subject to strict conditions – especially genital reconstruction, as this is an irreversible process.

In the case of trans men, genital reconstruction surgery is usually the last step in the transition process. When constructing a penis, the two chief methods are total neophalloplasty and

metoidioplasty. In the case of total neophalloplasty, pedicle flaps or free flaps are used to form the penis with the aid of neurovascular anastomoses. The penis constructed in this way is adult-sized and, following the implantation of a prosthesis, it may be suitable for penetrative intercourse, although one major disadvantage is significant scarring on the donor site. Metoidioplasty is the method of penis construction which uses local genital flaps to form a small penis from a hormonally hypertrophied clitoris. During the operation, the urethra is typically lengthened and perineo-scrotoplasty is also carried out, with the insertion of testicular implants. The neophallus constructed in this way has a masculine appearance and it enables urination in a standing position, but it is almost never adequate for penetrative intercourse (34).

2. OBJECTIVES

This thesis has four main objectives.

- To provide a historical overview of metoidioplasty.
- To give a detailed technical description of Belgrade metoidioplasty, which is a surgical modification specifically developed by the working group involved in this present study.
- To report on the working group's experiences with metoidioplasty in relation to 813 patients, with particular regard to the recording of the complications that arose and the effectiveness of the method, supplemented by patient satisfaction data.
- To discuss the urethral reconstruction options that may be employed during metoidioplasty, and to describe their results, mentioning the most common urethral-associated complications.

The working group hopes that this summary of its results and the conclusions drawn from them will provide a basis for the development of both domestic and international recommendations related to the topic.

3. MATERIALS AND METHODS

Between February 2006 and April 2020, the working group at the Belgrade Center for Genital Reconstructive Surgery performed one-stage operations known as “Belgrade metoidioplasty” on 813 trans men (ages: 18-58, mean age: 24.4). The surgery involved urethral lengthening, the removal of the vagina (colpocleisis), perineo-scrotoplasty and the insertion of testicular implants. The mean body mass index (BMI) of the patients was 24.6 (range: 16.4-32.8).

The selection criteria corresponded to those specified in version 8 of the WPATH Standards of Care (33): 1. Persistent, well-documented gender dysphoria (with a minimum of two referrals from qualified mental health professionals who have independently assessed the patient stating that transition therapies, including surgical therapies, are justified to improve the quality of the patient’s life); 2. A minimum age of 18, with the capacity to make a fully informed decision; 3. In the case of ongoing mental health or medical concerns, such concerns must be reasonably well controlled; 4. Twelve continuous months of hormone therapy (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones [in the current patient pool, no such exception was encountered]); 5. A minimum of 12 continuous months of living in a gender role that is congruent with their gender identity (87).

Adherence to the WPATH criteria is particularly important in order to minimize the likelihood of postoperative regret and the consequent risk of suicide (114). Psychiatric preparation is an important part of surgical preparations. The task of the surgical team is to familiarize the patient with the steps involved in the chosen type of surgery, as well as with other surgical options, their advantages and disadvantages, recorded results and potential complications. By comparing the patient’s realistic expectations with the alternatives, a joint decision must be made as to whether metoidioplasty can be considered as an option.

The surgical plan requires meticulous and customized elaboration in the case of each individual patient, taking into account a variety of criteria. In addition to the above WPATH criteria, the additional criteria recommended by the Belgrade Center are: 1. A BMI of below 30; 2. Appropriate anatomical features (the presence of labia minora, the integrity of skin flaps and their suitability for use); 3. Adequate local genital response to topical hormone therapy and/or genital vacuum treatment.

When considering candidates for metoidioplasty, patients’ preferences are also important, as some decline the use of oral mucosa, thus eliminating the risk of morbidities on the donor site, while others only accept the simplest tubularization technique, thus reducing the risk of possible complications inherent in graft urethroplasty. Although all candidates usually undergo systemic

masculinizing hormone therapy, hypertrophy thus being more or less characteristic of their genitals, this can be further enhanced by means of the topical application of dihydrotestosterone (DHT) and vacuum therapy (115, 116).

Before surgery, three months of DHT treatment combined with twice daily vacuum therapy is recommended. It is recommended that a vacuum pump be applied to the clitoris for 30 minutes twice a day according to the instructions. A general surgical recommendation is to discontinue both systemic testosterone and topical DHT treatment 14 days before surgery in order to reduce the risk of intraoperative bleeding or thrombosis (115).

All the aforementioned criteria were met by the current patient pool. The mean duration of hormone therapy before surgery was 32 months (range: 14-288 months). In each case, patient-specific surgical planning and implementation was employed. During urethral reconstruction, in addition to local, well-vascularized genital tissue and flaps, in some cases oral mucosa or other skin grafts were also used. Prior to metoidioplasty, 657 patients had undergone hysterectomy and bilateral salpingo-oophorectomy, while in 156 cases this was performed at the same time as the metoidioplasty. In 755 cases, a bilateral mastectomy had been performed prior to the metoidioplasty, while 58 patients underwent the procedure simultaneously with the metoidioplasty. In 46 cases, all three of the aforementioned interventions were performed at the same time.

In cases where the surgery entailed fertility issues, all patients were informed accordingly (hysterectomy and bilateral salpingo-oophorectomy result in irreversible infertility, and if the patient requests the cryopreservation of their gametes, this must be arranged before surgery). Postoperative quality-of-life and patient-satisfaction questionnaires were completed electronically.

The questionnaire included points regarding functional (urination, quality of erection, genital sensitivity, penetrative ability), aesthetic and patient-satisfaction criteria. In most of the questions, a five-point scale was used. (1: completely dissatisfied, 2: mostly dissatisfied, 3: neither satisfied nor dissatisfied, 4: mostly satisfied, 5: completely satisfied / 1: never, 2: rarely, 3: sometimes, 4: often, 5: very often). The document is a non-validated questionnaire developed by the Belgrade Center.

3.1. SURGICAL TECHNIQUES

The steps in the process of modern metoidioplasty are based on the latest anatomical knowledge of the female genital organs (56-58). Prior to the operation, elastic compression stockings are fitted on the patient and low molecular weight heparin (LMWH) is administered (a subcutaneous injection of enoxaparin sodium, its dosage calculated per kilogramme of body weight). Following anaesthesia, vancomycin is administered as an antibiotic prophylaxis. Following proper isolation and washing, a CH 16 silicone Foley urethral catheter is inserted, via which the bladder is filled and a suprapubic catheter is inserted for later urine diversion.

Following this, electrocautery is employed to perform a colpocleisis, with the exception of a small part of the anterior vaginal wall, which will be used for the subsequent reconstruction of the bulbar urethra. The remaining vaginal wall is closed with a thick and absorbable braided multifilament suture using circular stitches. A circular incision is made around the clitoris, continuing in two parallel vertical incisions beside the urethral plate. Following this, the suspensory ligaments of the clitoris are cut so that it is straightened and lengthened.

Based on the observations of our working group, although loosening the ligaments of the clitoris is the key to a successful metoidioplasty, its maximal distension can occasionally result in scrotalization of the neophallus, which, despite the tensility of the clitoris being increased, with the neourethra being longer, does not result in a real increase in penis length. If the urethral plate is short, it is infiltrated with 1 ml of a 1:100,000 adrenaline solution at the level of the crown of the clitoris, and then the urethral plate is incised transversely, which results in a further increase in length. In the reconstruction of the urethra, the first element to be formed is the bulbar urethra, as a continuation of the original urethral opening, for which the preserved anterior vaginal wall flap is also used. During urethral reconstruction, 5-0 absorbable monofilament suture is used.

On the other sections of the urethra, several types of urethral reconstruction are possible: simple tubularization (Group A, n = 92); intact urethral plate + labia minora or dorsal clitoris onlay flap (Group B, n = 42); urethral plate augmented with oral mucosa + dorsal clitoris onlay flap (Group C, n = 83); urethral plate augmented with oral mucosa + labia minora onlay flap (Group D, n = 537); urethral plate augmented with labial skin graft + dorsal clitoris/labia minora onlay flap (Group E, n = 59). The selection of the optimal surgical technique may primarily depend on specific anatomical features (the quality of usable tissues and flaps), but it may also be based on the patient’s preference, as mentioned earlier in this chapter (in the current case study, no personal preferences were indicated).

3.1.1. SIMPLE TUBULARIZATION OF THE URETHRAL PLATE (GROUP A)

During the procedure, the simple tubularization of the well-developed, adequately tensile urethral plate is performed over a silicone catheter. In order to reduce postoperative complications, the suture lines should be covered with well-vascularized local tissue. The procedure is not recommended in cases where the urethral plate is too short even after the suspensory ligaments of the clitoris have been cut.

3.1.2. URETHROPLASTY USING WELL-VASCULARIZED GENITAL FLAPS (GROUP B)

The urethra can be augmented with local well-vascularized genital flaps to create a neourethra of adequate diameter. The dorsal skin flap of the clitoris can be utilized, it being transposed ventrally using a buttonhole manoeuvre; alternatively one of the well-developed and well-vascularized, hairless labia minora flaps may also be used. With the aforementioned flaps, the neourethra can be constructed – with or without the transection of the urethral plate – with further graft augmentation. While maintaining the blood supply, the remaining part of the labia minora is used for subsequent penile skin construction.

3.1.3. GRAFT + FLAP URETHROPLASTY (GROUPS C, D & E)

During the procedure, in order to achieve an adequate urethral length, the urethral plate is transected and then lengthened with various grafts. In the majority of cases, oral mucosa grafts are used, as this is the “gold standard” for urethroplasty (117, 118). The oral mucosa is flexible, its shrinkage is negligible, it is resistant to many microorganisms, it is usually available in sufficient quantity, and the rate of scarring and complications on the donor site is minimal (118, 119).

If the development and tissue quality of the labia minora are adequate, the inner hairless part of one such flap can also be used as a graft. Following the transection of the urethral plate, it is usually necessary to cover the 3-6 cm-long tissue gap with a graft. It is recommended that the graft be fixed to the cavernous bodies of the clitoris with several stitches in order to ensure the survival of the graft and reduce the risk of postoperative hematoma formation.

As mentioned previously, the ventral part of the urethra can be constructed from a dorsal clitoral skin flap or a hairless, well-vascularized labia minora flap. The dorsal and ventral parts of the neourethra are joined over a CH 12-14 silicone Foley catheter. In general, the use of the labia

minora flap is preferred for the ventral neourethra, since it is hairless and the rate of complications related to its use is adequately low (120, 121).

If its use is necessary, the oral mucosa is generally harvested from the buccal surface of the left cheek, but the contralateral buccal surface, the sublingual mucosa, or the inner mucosa of the lower and upper lips are also satisfactory alternatives. After standard mucosal disinfection (using an undiluted antiseptic solution containing octenidine dihydrochloride and phenoxyethanol), the necessary mucosal dimensions are marked in an ellipse, and then the designated area is infiltrated with 1 ml of a 1:100,000 adrenaline solution.

It is important that the designated area does not fall close to the parotid duct and the pink outer surface of the lips. The graft must be mobilized in the layer above the muscle, and then the fatty tissue must be removed from its surface. Following haemostasis, the donor site is closed with a 3-0 absorbable suture (a braided multifilament sterile surgical suture of polyglactin 910 copolymer). In certain cases, a satisfactory alternative to an oral mucosa graft is a local labia minora skin graft, which – if it is available in adequate quality and quantity – is prepared from the hairless medial surface.

Use of a labia minora skin graft can reduce the risk of oral complications. The graft is placed on the defect sustained by the urethral plate, and it is also fixed to the edges and the base with a 5-0 monofilament absorbable suture (a synthetic monofilament suture made of gluconate) to construct the dorsal segment of the neourethra. The ventral part of the neourethra is constructed by mobilizing a well-vascularized labia minora flap or, in the case of underdevelopment or poor tissue quality, a well-vascularized dorsal clitoral skin flap, and transposing it with a buttonhole manoeuvre.

One of the aforementioned well-vascularized flaps is joined to the dorsal part of the neourethra with a 5-0 absorbable monofilament suture (a synthetic monofilament suture made of gluconate) over a CH 14-16 silicone Foley catheter. The suture lines are covered by the vascularized tissue elements of the flap, which reduces the risk of complications. If the length and tensility of the urethral plate is adequate, graft augmentation can be omitted. In certain cases, if the urethral plate is adequately broad and tensile, a simple tubularization of the urethra can be performed using a 5-0 monofilament suture over a CH 14 silicone Foley catheter.

To reconstruct the glans, two vertical incisions are made to suitably mobilize the glans wings, which are then closed without tension over the catheter, thus creating the neomeatus and neoglans. An important consideration for complete reconstruction is tension-free sutures and covering with well-vascularized tissue. The remaining unused healthy skin flaps of the labia minora and clitoris are

then used to construct the skin of the neophallus, with due care paid to the integrity of their blood supply.

A well-defined penoscrotal angle should be created by the proper rotation of the flaps. For suitably aesthetic results, it must be ensured that the penis is not scrotalized, which results in a loss of relative length. After the insertion of a perineal drain, the perineum is closed in layers. During perineo-scrotoplasty, the scrotum is formed from the labia majora. A bilateral incision is made and the cavities for the testicular prostheses are prepared by blunt dissection. After careful haemostasis, suitably sized testicular prostheses are implanted into the subcutaneous pockets.

The prostheses can also be implanted from the midline, but this heightens the risk of possible complications, since in the event of a complication, they can more easily come into contact with urine, which increases the chance of the implants being rejected. Thus, the implantation of testicular prostheses via two separate hemiscrotal incisions was generally preferred by the working group. The subcutaneous pockets are irrigated with an antibiotic solution (two ampoules of 80 mg gentamicin injection diluted with 100 ml standard 0.9% sodium chloride solution), and after the well-positioned prostheses have been implanted, the hemiscrotal incisions are closed with absorbable suture material.

A loose compression bandage is placed on the neophallus (a 4 cm wide self-adhesive elastic bandage made of viscose, cotton and polyamide). Post-surgery, the patients receive combined cephalosporin and metronidazole antibiotic therapy (a 2 g ceftriaxion infusion once a day, a 500 mg metronidazole infusion twice a day), as well as anticoagulant therapy (subcutaneous use of enoxaparin sodium, dosage per kilogram of body weight according to the prescription).

Systemic testosterone treatment can be resumed on the third day after surgery. After hospital discharge, prophylactic LMWH treatment (subcutaneous use of enoxaparin sodium, dosed per kilogram of body weight according to the prescription) and oral cephalosporin therapy are recommended until the removal of the urethral catheter. On average, the drains are removed on the third day after surgery, and the urethral catheter/stent is removed after seven to ten days, while the suprapubic catheter is removed after three weeks. Check-ups were performed in the third, sixth, and twelfth postoperative months after the removal of the suprapubic catheter, and annually thereafter.

During the follow-up, urinalysis, uroflowmetry, ultrasound examinations, and, in some cases, urethrocystoscopy were performed. Patients also filled out a non-validated postoperative satisfaction questionnaire developed by the Belgrade Center. The test data was aggregated with the

SPSS 20.0 software package (IBM Corp., released 2011, IBM SPSS Statistics for Windows, 20.0 version 2.0. Armonk, NY: IBM Corp. R 3.4.2 (R Core Team, 2017)).

4. RESULTS

The mean postoperative follow-up time was 94 months (range: 16-180 months). The mean length of the trained penis three to six months after surgery was 5.6 cm (range: 4.8-10.2 cm). The mean operative time was 170 minutes (range: 112-217 minutes). The mean hospitalization period was three days (range: 1-5 days). On average, the drains inserted during surgery were removed on the third postoperative day, with the urethral stent being removed on the tenth day, and the suprapubic catheter being removed after three weeks. The optimal urethral diameter was checked by means of urethrocystography and uroflowmetry.

The mean maximum urinary flow rate (Qmax) value was 21.6 ml/s (range: 16.9-27.2 ml/s). Postoperative complications can be grouped into minor ones (e.g.: hematomas, infections, minor skin necrosis, urinary tract infections, mild urinary complaints, and small urethral fistulas) and major complications (e.g.: serious skin necrosis, fistulas, urethral strictures, and implant displacement or rejection). In the case of the major complications, additional surgical corrections are usually necessary. The results reported here do not address complications associated with mastectomies, but their proportion corresponded to the data recorded in the literature (122).

Following gynaecological surgery, hematoma formation occurred in one case, which was cured by conservative treatment. In metoidioplasty operations, the most frequent complication was related to the reconstruction of the urethra (n = 86, 10.55%). Urethral fistulas were detected in 8.85% and urethral strictures in 1.7% of cases. **Table 1** shows the percentages of fistula and stricture distribution in the previously detailed surgical groups.

Of the fistulas, in 63.88% (n = 46) cases the fistula developed at the level of the anastomosis. 71.42% of the strictures were also present in this location, i.e. at the level of the anastomosis. The fewest fistula complications were observed in Group D, where the urethral plate was augmented with oral mucosa and the ventral urethra was formed from a well-vascularized labia minora flap. The proportion of strictures was also the lowest in Group D (on a level with Group A).

In all five groups, the surgical success rate exceeded 80%, with the overall success rate regarding the urethra and urination at the time of the 12-month check-up being 89.45%. Regarding testicular prostheses, rejection was observed in 17 cases (2%), while displacement occurred in 26 cases (3.2%). Perineal cyst formation or perineal discharge was observed in 78 cases (9.6%). Of these latter complications, those which persisted longer than six months were solved with minor surgical corrections between six and 12 months after the original operations.

No further major complications were observed in connection with the metoidioplasty operations. Regarding all complications, the proportion requiring revision surgery was 21.77% (n = 177). This figure includes not only the surgical correction of urethral complications, but also other non-urethral-associated revisions, including, in the case of one-stage combined techniques, surgical revisions of complications following bilateral mastectomy, and hysterectomy and bilateral salpingo-oophorectomy.

In the below table, only the urethral complications are summarized since our chief topic is the analysis of urethral reconstructions, and the comparison of other complications was not considered relevant due to the small sample size. In the case of minor complications, the rate of dysuria (dripping, spraying) was 14.63% (n = 119), while the incidence of urinary tract infections was 5.04% (n = 41). The patients concerned were satisfied with the results of the additional surgery and the surgical wounds healed without complications. Postoperative vacuum therapy on the neophallus was recommended to all patients.

The postoperative questionnaire was completed by 655 patients (80%). The majority were satisfied with the cosmetic results (79% completely satisfied, 20% mostly satisfied, 1% dissatisfied). All patients reported good tactile and erogenous sensation. Among those with an active sex life, the size of the penis was reported to be inadequate for penetrative intercourse. Unimpaired clitoral sensitivity and full erectile ability was preserved in all cases. No patient reported an inability to achieve orgasm, problems during the arousal phase, or issues with masturbation. Following surgery, urination in a standing position became possible for all patients, even those with the highest BMI values.

Following metoidioplasty, 76 patients (9.35%) requested secondary phalloplasty. In 62 cases, latissimus dorsi free flap phalloplasty was performed, and in 14 cases abdominal flap phalloplasty was carried out. According to their feedback, not one patient regretted the operation. Those requesting total secondary phalloplasty cited the desire for better sexual functioning and a more natural appearance as their reasons.

Table 1: Complications and effectiveness in the different urethral reconstruction groups.

Type of urethral reconstruction (groups)	Number of cases (n)	Mean maximum flow rate (Qmax., ml/s)	Fistulas (n, %)	Strictures (n, %)	Success rate (n, %)
Group A	92	20.5	8 (8.70%)	1 (1.10%)	83 (90.20%)
Group B	42	22	6 (14.30%)	2 (4.75%)	34 (80.95%)
Group C	83	21.4	9 (10.85%)	2 (2.40%)	72 (86.75%)
Group D	537	27.2	44 (8.20)	8 (1.50%)	485 (90.30%)
Group E	59	16.9	5 (8.50)	1 (1.70)	53 (89.80)
Total	813	21.6	72 (8.85)	14 (1.70)	727 (89.45)

5. DISCUSSION

Transgender treatment requires a multidisciplinary approach. Well-functioning working groups need more mental health specialists (psychologists and psychiatrists), endocrinologists, surgeons (urologists, gynaecologists, plastic surgeons and microsurgeons) and social workers. The number of gender affirmation operations is increasing very rapidly worldwide. The multidisciplinary experience of the past 100 years regarding trans healthcare has clearly improved the effectiveness and quality of its provision.

With its 40 years of experience, the Belgrade Center, which focuses on gender dysphoria and genital reconstruction, is a leader in the development of trans healthcare, and its activities have made it one of the most renowned and respected such institutions in the world. A large part of the literature related to metoidioplasty became known as a result of the work of the Belgrade Center, which is why most people call the technique in question “Belgrade metoidioplasty” (90).

Although the treatment of gender dysphoria, and the challenging discipline of which it is a part, is still in its early years, it is developing very dynamically. Its principles are discussed in the current WPATH Standard of Care (33). Such guidelines are being constantly refined and improved, and new, updated guidelines are periodically formulated, which are generally accepted by the largest centres for gender dysphoria. The guidelines make empirical findings in order to suitably improve the mental health, hormonal, and social treatment of transgender people and consequently enhance their quality of life in general, psychosocial and sexual terms alike (123-127). At the time of writing, in Hungary there are no unified national guidelines for trans healthcare in the Hungarian language. The need for this in the future is manifest.

During transition, as a first step in terms of health, it is essential to obtain the opinions of mental health professionals which confirm a diagnosis of gender dysphoria. It is important to rule out other psychiatric conditions that can mimic gender dysphoria (e.g. schizophrenia, etc.). A misdiagnosis can entail very serious consequences, and lead to suicide attempts or even death. The next step in medical gender affirmation is hormone therapy, which helps individuals gain “real life experience” in their desired gender role.

This stage is considered to be more or less reversible, while surgical therapies, especially in the final stages of transition (genital reconstructions), are generally considered to be irreversible. Not all patients go through the entire transition process. Each transition requires customized surgical planning, and healthcare professionals must listen to the patient’s needs and explain the opportunities, results and possible complications.

In almost every case, the requirements for genital reconstructive surgery are a minimum of one year of preventive hormone therapy and independent referrals recommending surgery from two mental health professionals. In the case of trans men, the final goal of transition may be the creation of a uniform male appearance together with a stable mental health status, a satisfactory quality of life, the weakening of female secondary sexual characteristics (and consequently the strengthening of male secondary sexual characteristics), the removal of the female genital organs and the aesthetic and functional design of the constructed male genital organs.

Not only does the transition process itself consist of several stages, but so does the surgical therapy in general (hysterectomy, bilateral salpingo-oophorectomy, bilateral mastectomy, neophalloplasty). With an experienced team, it is even possible that the surgical stages can be performed over the course of a single operation (91, 128). Combined one-stage operations require the establishment of experienced multidisciplinary surgical teams (consisting of urologists, gynaecologists, plastic surgeons, vascular surgeons, etc.) (34).

Most frequently, the first stage of surgical therapy is bilateral mastectomy. In the initial phase, having breasts causes the strongest dysphoria for most individuals, and this operation is often performed even before the commencement of hormone therapy, a solution which is provided for in the professional guidelines. In many countries, a precondition of legal gender recognition is the removal of the gonads. Despite this, according to the guidelines and the literature, many transgender people have no wish for genital surgery or surgical reconstruction. For some, the procreation of their own offspring is also extremely important (33).

Postoperative regret and dissatisfaction can manifest themselves to varying degrees, and – rarely – they may lead to suicide, which is considered to be the most serious complication of gender affirmation therapies. In the present study, not one patient regretted the intervention. This topic has recently been the focus of much research (114, 129). If an individual expresses a wish to return to their birth sex, they may well adjudge the therapeutic stages they have been through to be a mistake and even question the accuracy of the initial diagnosis. This confirms the validity of the concept that, in order to minimize complications, all transgender people require customized therapy in line with uniform systems of criteria.

The key to the effectiveness of gender affirmation operations is the precise selection of the patients, the provision of detailed preoperative information, the formulation of realistic expectations and the application of systems of uniform criteria. The construction of a neophallus is a very complicated process for trans men. An example of a one-stage alternative to phalloplasty is metoidioplasty.

In the USA, simple metoidioplasty is used relatively frequently. In spite of this, experiences reported in the literature are scarce (90). Over the years, there have been descriptions of many techniques involving a low number of cases or a short follow-up period, after which further publications concerning the given technique cannot be found. Due to this, the spread of such techniques (e.g. ring metoidioplasty, extended metoidioplasty) was inhibited (91, 92).

Previously, research involving the longest follow-up time was published by Hage, but with his technique, an average of 2.6 operations were needed to achieve a satisfactory result (78). Later, the largest number of cases and the longest follow-up periods for metoidioplasties were published by the Belgrade working group (80, 84-88, 90, 99). To the best of the author's knowledge, the present study is among those which report on the largest number of patients and the longest follow-ups.

The above finding has been confirmed by several working groups, such as the systematic meta-analysis of the Harvard authors (130). The assessment indicators of the Belgrade working group are similar to those in the literature regarding penis length, hospitalization period and duration of surgery (80, 88, 89), and the sexual satisfaction indicators are similarly high (78, 84, 85, 88, 89, 131-136). Most studies have focussed on trans women, and even those involving trans men have dealt mostly with total phalloplasty (137). Klein and Gorzalska showed a general improvement in quality-of-life, satisfaction and sexual life indicators following surgery (138). Interestingly, in many publications, the satisfaction indicators of the complication groups are similar to those of individuals who experience no complications (124, 125, 137). Although no statistical analysis was performed, this is supported by the present research findings.

The main disadvantage of metoidioplasty is the small neophallus it produces, which is not suitable for penetrative intercourse. Some patients therefore desire secondary phalloplasty. In the present study, the rate of secondary penis construction was 9.35%, the main reasons for which were the desire for a larger neophallus and for penetrative intercourse. This rate corresponds to the data in the international literature (8.5-24%) (78, 85, 87, 88, 91, 134).

The great advantage of Belgrade metoidioplasty is that it enables urination in a standing position in such a way that, in addition to the ability to experience an erection, the erogenous sensation of the penis is preserved. Maintaining the sensitivity of the clitoris is the basis for high sexual satisfaction and an enhanced quality of sexual life. Modern anatomical knowledge has shed light on the course of the clitoral dorsal neurovascular bundle and clitoral nerves, which is a condition for the maintenance of good innervation and sensitivity (58, 59, 139).

A high BMI index, an unfavourable physical build, or a limited response to hormone therapy negatively affect the effectiveness of metoidioplasty. A number of plastic surgery techniques, local hormone preparations, or the use of vacuum therapy can improve satisfaction rates and reduce instances of complications. The functional and aesthetic results of the surgery are all affected by responsiveness to topical DHT and systemic testosterone treatment, and vacuum therapy, while additional factors include anatomical attributes, tissue quality, preoperative preparation (realistic expectations), patient preferences, body weight (below BMI 30), and the patient's physical build (central obesity, aesthetic disorders due to excessive weight loss, and too much fatty tissue in the area of the mons pubis are all detrimental) (118, 140).

The observations regarding DHT treatment are confirmed by the results of hypospadias operations (115, 116). The patient pool met the specified criteria; only those for whom the working group considered the technique to be an ideal choice for the construction of a penis were included.

In order to avoid undesirable effects, such as prolonged bleeding or an increased risk of thrombosis, it is important to terminate topical hormone treatment at least 14 days prior to surgery (115). A prolonged duration of surgery may also result in greater blood loss, which may increase the risk of the need for transfusion and other complications, and may lead to prolonged, complicated hospitalization (141, 142).

Vacuum treatment plays an important role not only in the preparation for surgery, but also in the postoperative period, as it helps to prevent scarring in the neophallus and its postoperative retraction. Vacuum treatment is recommended for at least 6-12 months after surgery, for this purpose the working group has designed a simple vacuum pump that can be made by anybody.

Although it is evident that in terms of technique and effectiveness, metoidioplasty has developed dramatically in recent years, its principles have remained the same: the construction of a small neophallus from a hormonally enlarged clitoris. As a result of development, this method of penis construction is now popular worldwide (141).

Belgrade metoidioplasty was the first to use the innovative method whereby the urethra is constructed as far as the tip of the neophallus in a one-stage procedure. The basis for this was also established by experiences gained in the surgical correction of clitoromegaly (143). Headway was made in increasing the length due to a better understanding of the anatomy of the clitoris. With the cutting of the suspensory ligaments of the clitoris and the transection of short urethral plates, the dimensions of the neophallus can be further increased, but the final size still largely depends on the initial size of the clitoris before surgery (83, 88, 118).

Although the radical loosening of the suspensory ligaments of the clitoris is important, a recent observation notes that too radical a loosening can in some cases lead to the scrotalization of the neophallus, which does give not a real increase in length, and can even result in a shorter useful penis length both optically and functionally (119).

The most common complication arising from the removal of the female genital organs is the development of a perineal cyst, the cause of which can be the formation residual mucus due to the inadequate destruction of the vaginal mucosa, an inflammatory process, bleeding or a fistula.

Generally, only small cysts develop, but it is not uncommon for a painful cystic mass to appear in the perineum, growing almost along its entire length. This can cause protracted dysuria, inflammatory symptoms and severe pain, and result in a consequent deterioration in the quality of life. The surgical removal of such cysts is necessary in almost every case.

Larger perineal cysts often communicate with the neourethra. In the present study, all perineal cysts were eliminated by means of revision surgery. Bleeding or other complications related to hysterectomy and bilateral salpingo-oophorectomy are rare, and the present study experienced only one complication involving postoperative bleeding and the formation of a hematoma, which healed following conservative treatment.

Based on the data in the literature, the rate of complications associated with mastectomy is 12.5% (122), which is similar to the experience of the present study, but due to the topic of this thesis, these results are not discussed in detail. Although combined operations with an experienced surgical team are not associated with a significant increase in complications (89), even in the case of simple metoidioplasty, the choice of a team with extensive surgical experience is highly recommended (34, 144).

The rate of complications following metoidioplasty is lower than that following total phalloplasty (135). In urethroplasty, which is the most challenging field of all, groundbreaking results were achieved by using all the locally available well-vascularized genital tissue to construct the neourethra, thus making urination in a standing position possible in a one-stage procedure (85-89, 90, 134).

An additional innovation and advantage is the extensive surgical experience gained with hypospadias, epispadias, bladder extrophy, and other sexual differentiation disorders (84-86). In the course of its development, various reconstructive manoeuvres, vascularized flaps, and grafts have all come to play a role in metoidioplasty (83, 145). As the “gold standard” for grafts, the oral mucosa is tensile, pliant and not susceptible to infections; over time it is capable of assuming the

characteristics of the urothelium, and it is additionally available in large quantities, cost-effective and associated with a low number of donor-site morbidities (93, 95-97, 119).

Concerning urethral complications, use of the vaginal wall flap in the bulbar segment can be seen as a positive development. Based on the data in the literature and the professional experience of the working group, the use of very long vaginal flaps for urethral reconstruction should be avoided, as the characteristics of the vaginal mucosa (its natural folds) pose a greater risk of complications (91, 118).

Urethral and other complications displayed almost the same rates in the different groups in the study. According to the data in the literature, the rate of complications varies between 11% and 35% (78, 83-88, 90), although some publications even report rates of over 40% (78, 91). According to the data in the literature, the frequency of fistulas is 7-14% (84-86, 88, 90), but even higher fistula rates can also be found (78). Djordjevic previously analyzed urethroplasty in two separate groups, and his results proved that the urethral plate augmented with an oral mucosa graft and labia minora flap was the most effective in terms of urinary function (88).

Like urethral strictures, fistulas most often develop at the level of the anastomosis of the original urethral opening and the neourethra. At this point, an approximately CH 20 urethra continues into a CH 12-14 urethral diameter, and thus a relative urethral narrowing is experienced. The pressure of urine flow is also the highest here, making this locus the weakest point as well. It is therefore very important to create a suitable funnel-shaped structure and to cover the anastomosis with an extra layer of well-vascularized tissue, which is harvested from the surrounding, well-vascularized connective tissues and the bulbar muscle (145).

In the present study, 63.88% (n = 46) of the fistulas developed in the above locus, at the level of the anastomosis. Based on the team's observations, strictures in the bulbar segment are also significantly more frequent (71.42%, n = 10) than pendular urethral strictures. In virtually all cases, these urethral strictures could be treated with revision surgery, while more than three quarters of pendular strictures were successfully treated conservatively with dilation. Due to the patient-specific anatomy and the combined use of numerous flaps, surgery for urethral strictures requiring revision is extremely challenging, even for highly experienced genital reconstruction surgeons. In consequence, each case requires a customized surgical plan, although unfortunately no general guidelines exist (146). From the above, the working group established that the treatment of more proximal urethral strictures and fistulas usually requires surgery. Fistulas located more distally may heal spontaneously, and more distal strictures may respond well to a single dilation or may heal following urethrotomy (145, 146). In relation to the analysis of complications, in the present study

the most successful urethral reconstruction method was the urethral plate augmented with oral mucosa and a labia minora flap, which is a confirmation of previous findings (88, 119).

The effectiveness related to urination in the present study is also very high: 98-100% (85, 88, 119). The majority of techniques in the literature have good results in this regard, with the exception of ring metoidioplasty, where it is only 67.5% (91). Most methods do not perform the complete reconstruction of the urethra in a one-stage procedure; thus it is understandable that there is a significant lack of data on urination in a standing position, regardless of the technique employed. In Belgrade metoidioplasty, similarly good Qmax values can be achieved with all of the different urethral reconstruction options.

The suitability for penetrative intercourse of the neophallus constructed in the course of Belgrade metoidioplasty falls short of that formed during phalloplasty, the former possessing limited penetrative ability or none at all. Its great advantage, however, is the preservation of naturalness, sexual spontaneity and erogenous sensation due to the use of local tissues. The fundamental disadvantages of phalloplasty – high cost, multistage intervention, lengthy duration of surgery, longer period of hospitalization, high surgical risk and complication rate, difficult handling of prostheses and the possibility of their malfunction, loss of sexual spontaneity, scars which distort the donor site and are unsightly – can be eliminated or greatly reduced if the patients treated are both well selected and suitably motivated (84).

Among the methods described in this study and applied in practice, Belgrade metoidioplasty is the technique that enables complete reconstruction in a one-stage procedure (147) and, depending on the length of the urethra, a neophallus of 3-10 cm can be formed. Regarding the mean penile length, the 5.6 cm achieved by the working group is similar to the mean results of other authors (134) and the same as the previous results of the working group (84, 85, 88). With regard to the length of the neophallus, Cohanzad boasts the best results, but the number of cases is extremely low (n = 10), and he employs a complicated postoperative penile traction device, which, due to its complexity, has failed to gain wider usage (92). In general, the greatest neophallus length was observed in cases of graft-augmented urethral plates. In the case of the present study as well, the longest neophalluses were almost without exception in Group D.

The main goal of metoidioplasty is to create a genital organ with a realistic and masculine appearance that enables urination in a standing position, with preserved tactile and erogenous sensation, in order to improve the quality of a patient’s life. Although the drawbacks of total phalloplasty are well known, there is still no truly satisfactory penis construction option for either cis or trans men. A promising alternative in the future may be penile transplantation, but as yet

extremely few successful operations have been carried out, and experience, which is limited to cases of cis men only, is thus negligible (148). The procedure is very complex and, in addition to the technical obstacles, it raises many ethical problems. Despite this, it is to be hoped that in the future, penile transplantation may open new possibilities in genital gender affirmation surgery.

6. CONCLUSIONS

In the case of FtM transgender, metoidioplasty is a gender-affirming surgical option for patients who desire masculine external genitalia, but accept that the size of their neophallus will be less than that of an average male adult. The operation presents an opportunity to circumvent multistage phalloplasty. At the time of writing, there is currently no ideal metoidioplasty method.

With well-selected patients and an experienced surgical team, functional and psychosexual results are good. Essential factors for successful operations are suitable preoperative planning and preparation, and the provision of detailed information to the patient, as well as professional knowledge of anatomy and reconstruction. The method's current technical capabilities enable the construction of an aesthetic penis which ensures urination in a standing position. Moreover, sexual functions can be preserved or even improved, and thus both the functional and cosmetic results of metoidioplasty are acceptable.

High patient satisfaction and a short hospitalization period can be achieved with a relatively low complication rate. In the case of centralized care, it can be a practicable, safe, time-saving and cost-effective method. It preserves or improves sexual functions, and choosing a centre with sufficient experience guarantees an acceptably low risk of complications.

Patients must always be informed that the chief drawback of the method is that in the vast majority of cases the neophallus is not suitable for sexual intercourse. For patients who later desire total phalloplasty, any known method can usually be employed. Among the urethral reconstruction techniques utilized in the course of metoidioplasty, a neourethra formed from the urethral plate augmented with oral mucosa and a labia minora flap provides the best results.

Vacuum therapy and preoperative DHT treatment can significantly improve the effectiveness of surgery. Metoidioplasty can be used simultaneously with other gender-affirming surgical interventions (bilateral mastectomy, hysterectomy and bilateral salpingo-oophorectomy) without a significantly increased risk of complications and it thus offers patients a one-stage surgical transition.

There is currently no ideal solution for the construction of a neophallus and consequently long-term follow-up is recommended in all cases in order to further improve results and surgical techniques. During FtM gender-affirming genital surgeries, it is essential to take complex needs into account, and it is thus manifest that recourse to only one surgical method cannot be the key to success.

In order to improve the quality of trans healthcare, the establishment of trans-health centres is a top priority at both domestic and international levels. Vital factors in the potential establishment of such centres include the given surgical team's extensive experience in reconstruction, a substantial amount of previous cases, the involvement of an adequate number of competent specialists, the use of uniform international guidelines and systems of criteria, and international cooperation with other trans-health institutions.

7. NEW SCIENTIFIC FINDINGS

- As there is no comprehensive scientific literature on the topic, I consider this study to be of particular importance.

- Many urethral reconstruction methods can be used successfully during metoidioplasty, this study can assist the formulation of customized surgical plans and the selection of the appropriate reconstruction technique.

- Although the penis that can be constructed with metoidioplasty is not suitable for penetrative intercourse, in virtually all cases it enables urination in a standing position, which clearly improves patients' quality of life. Choosing the most suitable method of urethroplasty may also result in an increase in the length of the neophallus, and it can thus contribute to the improvement of the aforementioned indicators.

- The express advantages of metoidioplasty are the preservation of sexual spontaneity and erogenous sensation, and the guarantee of a natural result through the use of local flaps. With the development of newer urethroplasty procedures, a greater variety of local flaps may come to be utilized, but their selection and use must never compromise the achievement of the aforementioned primary goals. With the methods mentioned in this study, those goals are entirely feasible.

- Following the urethral reconstruction options detailed earlier, if necessary, any type of secondary total phalloplasty can be successfully performed.

- At present, Belgrade metoidioplasty, featuring any of the urethral reconstruction techniques presented in this study, is the only method that can provide complete genital reconstruction for trans men in a one-stage procedure.

- Belgrade metoidioplasty involving any of the recommended urethral reconstruction techniques can be successfully combined with other interventions, thus creating the possibility of a one-stage, complete surgical transition (hysterectomy and bilateral salpingo-oophorectomy, bilateral mastectomy, metoidioplasty) for well-selected patients.

- Regarding urethral reconstructions performed by metoidioplasty, no literature has been found reporting a larger number of cases or longer follow-ups than those of the Belgrade working group, upon whose results this study is based. This may be salient in the event of the development of future guidelines.

- With regard to the urethral reconstruction procedures employed in the course of metoidioplasty, this study can help with appropriate patient selection, preoperative preparation and postoperative rehabilitation. It can also contribute to the understanding and mitigation of complications, and the appropriate treatment of any complications which do arise.

- This study's findings establish that the treatment of more proximal urethral strictures or fistulas typically necessitates surgery. Fistulas located more distally may heal spontaneously, and more distal strictures may respond well to a single dilation or may heal following urethrotomy

- The results of this study and the endeavours of the specialists of the Belgrade working group may provide a good basis for the future establishment of a pioneering trans-health centre in Hungary. By means of the therapeutic and educational activities of multidisciplinary working groups or centres, the quality of life of trans people could be greatly improved, and their social exclusion and stigmatization could be significantly reduced.

8. PUBLICATIONS AND LECTURES RELATED TO THE TOPIC OF THE PRESENT THESIS

8.1. FIRST AUTHOR PUBLICATIONS

1. Bordás N, Kojovic V, Bizic M, Stojanovic B, Djordjevic M. Nőből-férfi nemi megerősítő műtét: metoidioplasztika – 6 beteg eredményeinek ismertetése [Female-to-male Gender Affirmation Surgery: Metoidioplasty – A Description of the Results of Six Patients]. Magyar Urológia [Hungarian Urology], Volume XXXI, Issue 1, 2019, pp. 9-12.

2. Bordas N, Stojanovic B, Bizic M, Szanto A, Djordjevic ML. Metoidioplasty: Surgical Options and Outcomes in 813 Cases. Front Endocrinol (Lausanne), 13 Oct 2021; 12:760284. **IF: 5.55.**

3. Bordás N, Stojanovic B, Bizic M, Szántó Á, Djordjevic ML. Metoidioplasztika szövődményei [Complications in Metoidioplasty]. Magyar Urológia [Hungarian Urology], 2022 (1), pp. 2-7.

8.2. CO-AUTHOR PUBLICATIONS

1. Bizic M, Stojanovic B, Bencic M, Bordás N, Djordjevic M. Overview on metoidioplasty: variants of the technique. Int J Impot Res, Nov 2020; 33(7):762-770. **IF: 2,896.**

2. Bizic M, Stojanovic B, Bencic M, Bordas N, Djordjevic M. Metoidioplasty as a one-stage phallic reconstruction in transmen. Plast Aesthet Res, 2020; 7:43.

8.3. LECTURES RELATED TO THE THESIS TOPIC

1. Bordas N, Stojanovic B, Bizic M, Kojovic V, Bencic M, Djordjevic M. Results and Trends of Gender Affirmation Surgery in Hungary. WPATH Symposium 2018, Buenos Aires, Argentina.

2. Dr. Noémi Bordás. Transzegészségügy: hormonterápia és nemi megerősítő műtétek [Trans-health: Hormone Therapy and Gender Affirmation Operations]. 24th Pannon Endocrine Club Weekend 2019, Baja, Hungary.

3. Bordas N, Bizic M, Stojanovic B, Djordjevic M. Transgender Healthcare in Hungary. EPATH Symposium 2021, Gothenburg, Sweden.

4. Bordas N, Alvarez ML, Asquith L. Healthcare for Minors under Attack: Experiences from the UK and Hungary. EPATH Symposium 2021, Gothenburg, Sweden.

5. Dr. Noémi Bordás. A tranzíció endokrinológiai és sebészeti aspektusai [Endocrinological and surgical aspects of transition]. The Fundamentals of Affirmative Support Work with Transgender Clients, Hungarian Psychological Association, LGBTQ Division, 2023, online webinar, Hungary.

The bibliography for citations in this thesis booklet is included in the full PhD thesis.

9. ACKNOWLEDGMENTS

I would like to express my gratitude to all those without whose help my PhD thesis would not have been possible.

I am deeply indebted to my supervisors, Prof. Dr. Miroslav Djordjevic and Dr. Árpád Szántó, for their guidance and theoretical and practical instruction. They supported me from the very beginning and assisted my work with their outstanding professional experience and expertise. I am grateful that they have always encouraged my interest in trans medicine and that, recognizing the relevance of the topic and the importance of my results, they made it possible for me to present my work, in the hope that domestic trans medicine may begin to develop in Hungary.

I would like to extend my sincere thanks to the members of my working group, Dr. Borko Stojanovic, Dr. Marta Bizic, Dr. Marko Bencic, and the operating theatre and ward staff, for the opportunity to work together with them and for their unfailing help with all my questions. Our joint work made an essential contribution to both my thesis and professional publications.

I wish to thank all the staff of my public workplace, particularly my current head of department, Dr. Sándor Molnár, and my former head of department, Dr. Endre Holman. I could always count on not only their support, faith and inexhaustible encouragement, but also their sincere friendship. I am especially grateful to the hospital's Chief Executive Officer, Dr. Szabolcs Szepesvári, and its Medical Director, Dr. Csaba Ördögh, for their supportive attitude towards my work.

Thank you to Dr. Kinga Villányi, editor-in-chief of the journal "Hungarian Urology", for making domestic publications possible for the working group.

I must thank the head of the Doctoral School, Prof. Dr. Lajos Bogár, and my programme leader, Prof. Dr. László Pajor, for providing me with the opportunity to complete my thesis.

I owe special thanks to Bence Pap, who actively participates in the affairs of the domestic working group and undertook a major role in the shaping and editing of my manuscript.

I am much obliged to Paul Crowson for his painstaking help in the English translation and proofreading of this study.

Words cannot express the gratitude of the whole working group for the trust, appreciation and love of our patients, which always gave meaning to our endeavours.

Last, but not least, I would like to thank my family from the bottom of my heart. They have always trusted me, stood by me and given me their sympathetic support in the course of my studies.

Special thanks go to my mother and father for their loving care and enthusiastic encouragement. I thank my family for their inspiration, which has always spurred me on throughout my life, and without which my thesis would not have been possible. I am incredibly thankful to my husband, Gábor, for his love, and I owe him a particular debt of gratitude for the exemplary patience with which he has endured all our difficulties. I give my thanks to him not only for being a steadfast source of strength, but also for the great ideas and knowledge with which he has consistently supported me.

This thesis is dedicated to my late father, Béla Bordás, who always followed my work with great love and interest.