Outcome and Refinements of Gender Confirming Surgery

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OUTCOME AND REFINEMENTS OF GENDER CONFIRMING SURGERY

Hannes Sigurjónsson

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Outcome and refinements of Gender confirming surgery

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Introduction Gender dysphoria is a state in which the individual shows strong and persistent identification with the opposite sex. After thorough diagnostic assessment, the treatment includes gender confirming surgery (GCS). The efficacy and benefit of GCS has been advocated to effectively resolve the patient’s gender dysphoria as well as improve quality of life and psychosocial functioning. The aim of the studies described here was to assess surgical techniques, complications, quality of life and functional outcomes of GCS.

Patients and Methods Study I is a retrospective study of surgical outcomes for patients who underwent male-to-female (MtF) GCS over a 14-year period (n=205). Study II describes a prospective study (n=40) of vaginal depth after vaginoplasty performed using solely penile skin for intra vaginal lining. Factors predicted to correlate with poor outcomes were analyzed using a multivariate regression model. Study III is a prospective study (n=19), examining patient-reported outcomes on health-related quality of life. We used the Swedish version of the Short Form-36 Health Survey (SF-36), which measures QoL across eight domains. The questionnaire was distributed to patients pre-operatively, as well as 1.3 and 5 years post-operatively. The results were compared between the different measure points, as well as between the study group and the general population. Study IV is a cohort study (n=22) of the sensitivity of the neoclitoris and its patient-reported functionality. Tactile and vibratory sensitivity was measured with the Semmes-Weinstein monofilaments and the Bio-Thespiometer vibratory measurement device, respectively. A body image questionnaire was provided to patients and the patients were asked about orgasm, pain and general satisfaction with the surgery.

Results In study I, the most common short-term complications were bleeding (11%) and infection (10%). Other complications, such as wound dehiscence (2%), rectovaginal fistula (2%), pulmonary embolus (2%) and deep vein thrombosis (0%), were rare. In study II, the average neovaginal depth was 10.2 cm (range 1-16 cm). Noncompliance with dilation protocol (p=0.001) and postoperative complications (p=0.01) were associated with decreased vaginal depth. Neither circumcision nor age affected the outcome of vaginal depth. In study III, transgender women reported significantly lower quality of life in most dimensions when compared to the general population. One year postoperatively, there was a trend towards higher scores compared to the preoperative measurement point; however, these scores then declined. In study IV, the average pressure threshold for the neoclitoris was 12.5 g/mm² and the average vibratory threshold was 0.3 µm. The vast majority of the study participants could reach orgasm (86%), and reported satisfaction with having undergone GCS (88%).

Conclusions MtF GCS can be performed with a low rate of major complications. Using solely penile skin is sufficient to create the vaginal lining, although adhering to a dilation protocol is crucial to attaining sustained vaginal depth. Quality of life among MtF patients compared to the general population is improved one year after GCS, but then declines. The sensate neoclitoris has a protective tactile sensation, gives the patient erogenous sensitivity and the ability to reach orgasm in the majority of patients. Over all, the vast majority of patients who undergo MtF GCS are satisfied.
LIST OF SCIENTIFIC STUDIES
This thesis is based on the following studies that are referred to in the text by Roman numerals as indicated below.

I. Hannes Sigurjónsson, Johan Rinder, Caroline Möllermark, Filip Farnebo, T. Kalle Lundgren.
   Male to female gender reassignment surgery: Surgical outcomes of consecutive patients during 14 years.

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    Solely Penile Skin for Neovaginal Construction in Sex Reassignment Surgery.

III. Ebba K. Lindqvist, Hannes Sigurjónsson, Caroline Möllermark, Johan Rinder, Filip Farnebo, T. Kalle Lundgren.
     Quality of Life Improves Early after Gender Reassignment Surgery in Transgender Women.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>BIS</td>
<td>Body Image Scale for Transsexuals</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>FtM</td>
<td>Female-to-Male</td>
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<td>GCS</td>
<td>Gender confirming surgery</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>MH</td>
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<td>MtF</td>
<td>Male-to-Female</td>
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<tr>
<td>SF-36</td>
<td>Short form health survey of 36 items</td>
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<td>PE</td>
<td>Pulmonary embolus</td>
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1 INTRODUCTION

1.1 BACKGROUND

Gender dysphoria and gender identity disorder are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [1], and in the International Classification of Diseases, Tenth Revision [2] (ICD-10 F64. X).

Gender identity disorder is a state in which the individual shows strong and persistent identification with the opposite gender [1]. This can cause significant distress for the individual regarding both social and occupational perspectives. The feeling of being born in the wrong sex commonly leads to a strong desire to reject the physical gender characteristics of the anatomical sex [1, 3]. When compared to the general population, individuals with gender dysphoria have a higher rate of psychiatric co-morbidities, which is relieved with treatment [4-6].

Causes of gender dysphoria have historically been hypothesized to be psychological, biological or a mixture of both [7]. A role for sex steroid-related genes in the pathogenesis of gender dysphoria has been proposed [8]. A neurobiological cause for gender dysphoria has been suggested as the sexual differentiation of the central nervous system and genitals can progress in opposed directions. Further publications have advocated that a certain part of the brain (the central subdivision of the bed nucleus of the striae terminalis), a key player in controlling sexual behavior, is larger in men than in women, and that this area is of female size in male-to-female (MtF) gender dysphoric individuals [9].

The treatment of gender dysphoria through an established procedure of diagnostic assessment, hormonal therapy and surgical procedures has been formalized by the World Professional Association for Transgender Health in their Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People [10]. Accordingly, the National Board of Health and Welfare has recently published national standards of care for Sweden [11].

Gender confirming surgery (GCS) is one of the cornerstones of the treatment of gender dysphoria. In 1957, Sir Harold Gillies was one of the first surgeons to describe successful GCS in a transgender woman [12]. Along with his colleague, Dr. Ralph Millard, they used a skin flap technique to create a vagina. Since that time, numerous surgeons have described their techniques and refinements, as will be discussed further in the chapter concerning surgical techniques.
1.2 OUTCOMES AFTER GENDER CONFIRMING SURGERY

The benefits of GCS have been advocated by various authors. Many of these authors have reported that GCS effectively resolves the patient’s gender dysphoria as well as significantly improving quality of life (QoL), psychological functioning and the well-being of transgender patients [13-16]. Certain studies have reported that transgender individuals experience a lower QoL than the general population [17-19], even after GCS [18]. However, a few studies have not found any difference in QoL or psychological aspects when comparing transgender individuals to the general population [20-22]. One limitation of many of these studies is a small sample size. There is also a scarcity of prospective studies that follow patient’s QoL for a longer period of time [23].

Although the safety and possible complications of GCS have been studied, thorough reports on short-term complications are scarce [24]. The main surgical complications reported in GCS are bleeding, infection, thrombotic events, wound dehiscence and rectal injury [25-29].

Regarding the surgical techniques used in GCS, considerable debate exists regarding whether penile skin alone is sufficient to provide the lining for the complete vaginal depth required. Commonly, penile skin is used for lining a part of the neovaginal cavity, the remainder being lined with scrotal flaps or skin grafts [3, 30]. Disadvantages of using skin flaps and/or skin grafts, instead of solely penile skin, include the creation of intravaginal scars, the use of hair-bearing skin and rougher skin quality compared to the pliable and soft penile skin [27].

In addition to vaginal depth, one of the major goals of GCS is to reconstruct genitalia with tactile and erogenous sensitivity [26]. In genital GCS, the neoclitoris is made of the proximal dorsal section of the glans penis, harvested on a neurovascular pedicle. The provision of erogenous and tactile sensitivity of the neoclitoris in GCS was first described by Brown (1976) [31, 32] and is today used by the majority of gender surgeons performing GCS [33-39].

However, measurements of the sensory function of the neoclitoris and investigation of orgasmic function are currently limited to a few studies [33, 39, 40]. In particular, there is a lack of studies correlating objective measurements of clitoral functionality and patient-experienced outcomes. The available studies show that MtF transgender patients report a high rate of ability to reach orgasm. Erogenous sensitivity may also be present at other parts of the body, such as the vaginal introitus through nerves in the scrotal skin and perineal flap, and the penile shaft remnants through the internal part of the reconstructed vagina [33].
1.3 EPIDEMIOLOGY

In Sweden, the diagnosis coded as F64.0 (transsexualism) was applied to 1,127 patients in 2013. This was twice the number as that seen only three years earlier, and triple the number three years prior to that (unpublished data, personal correspondence with the National Board of Health and Welfare). This is the case for many countries in which the incidence of gender dysphoria seems to be increasing rapidly [41, 42]. Some countries have reported the prevalence of gender dysphoria and the application of GCS. In the Netherlands, the prevalence of gender dysphoria is reported to be 1:11,900 for MtF and 1:30,400 for female-to-male (FtM) [43]. In Belgium, it is 1:12,900 for MtF and 1:33,800 for FtM [44]. In Germany, 1:18,250 for MtF and 1:32,050 for FtM [45]. In Sweden, the incidence and prevalence have recently been calculated for a 50-year period (1960-2010) by Dhejne et al. [46]. The incidence increased significantly during this period, and the fastest increase was noted after the year 2000. The prevalence in 2010 was 1:7,750 for MtF and 1:13,120 for FtM in Sweden [46].
2 SURGICAL TECHNIQUES

A spectrum of surgical procedures exists for transgender women. In addition to genital surgery, these include breast augmentation, shaving of the prominent part of the trachea (chondroaryngoplasty), facial feminization surgery and hair removal. The creation of functionally and aesthetically pleasing feminine genitals remains one of the most difficult challenges for surgeons [26]. The main operative procedures used in GCS are orchectomy, penectomy, clitoroplasty, labiaplasty and vaginoplasty. Many techniques have been described for the creation of the vagina. The most widely-used techniques are penile or penile-scrotal skin flaps, skin grafts and pedicled small or large bowel segments [3, 47-50]. The penile or penile-scrotal technique is considered state of the art by many, and other techniques are only applicable in secondary cases [3]. In this thesis, the focus lies on vaginovulvar GCS. Below, our surgical technique that uses solely penile skin for the vaginal lining is described [51].

2.1 PRIMARY SURGERY

Under general and epidural analgesia, the patient is placed in the lithotomy position. A caudally-based scrotal flap is marked and raised sharply for surgical access to the perineal area. The bulbous musculature and parts of the bulb of the urethra are dissected off the proximal corpus spongiosa and discarded (Figure 1). Orchietomy is performed by bilateral ligation of the funiculi after dissection of each funiculus. Creation of a neovaginal vault in the area between the urethra and the rectum follows sharp dissection through the perineal musculature and the perineal raphe. Once past the raphe, dissection continues bluntly, under bimanual palpation, anterior to the Denonvilliers’ fascia towards the prostate, until sufficient depth and width is reached. A penile prosthesis (40 mm diameter x 130 mm length) is inserted to assure a sufficient neovaginal depth and width (Figure 2). The penile skin is then circumferentially incised along the proximal glans border and separated from the corpora; the penis is thereby degloved (Figure 3). This skin forms a cylindrical skin flap, a “pouch.” The prepuce-fold is dissected and this skin is used to increase the length of the pouch. The distal pouch opening corresponding to the foreskin area is closed by suturing, after which the skin-pouch is inverted (Figure 4). A triangular piece of the proximal dorsal glans penis is drawn out and dissected off the penis using a dissection plane superficial to the tunica albuginea, to preserve innervation and vascular supply to the erogenous tissue. Thus, a sensate flap is raised for use as a neoclitoris (Figure 2). The urethra is then completely dissected from the corpora and divided at a suitable length (Figure 3) before the penile remnants are amputated close to the symphysis at the radix penis, and each corpora cavernosa is ligated. The skin of the penis is invaginated into the neovaginal cavity and the posterior commissure sutured. This invagination (Figure 4) causes a
significant cranial pull of the skin, which causes the posterior commissure to rise upwards to cover part of the vaginal orifice. The pre-pelvic skin is likewise stretched and the anterior commissure consequently widened; we avoid extensive undermining of the pre-pelvic skin or the lower abdomen to preserve maximum vascularization to the penile skin. The penile skin is not anchored into the neovaginal space by suturing. Next, semicircular and rhomboid incisions cranial to the neovagina are performed and the neoclitoral flap and the urethra, respectively, are sutured into place (Figure 5). The lateral incisions are closed by suturing and the neovaginal cavity is packed with Vaseline gauze before bandaging (Figure 5). In case of bleeding or fecal contamination, the surgical area is inspected; otherwise, bandages are worn until the fourth postoperative day when dressings are changed and the urethral catheter is removed. Mobilization is allowed on postoperative days three to five. Vaginal dilation is commenced on the fifth or sixth postoperative day, and continues for a minimum of one year. The dilation regimen consists of initial dilation with a 25 mm-wide semi-rigid silicon dilator for 20 minutes, two to three times per day. After three weeks, the patient uses a rigid plastic dilator with a width of 35 mm. An example of the final result 12 months postoperatively can be seen in Figure 6.

Figure 1. The scrotal flap is marked (left) and raised (right). The neovaginal cavity is then dissected through the perineal raphe and musculature.

Figure 2. A plastic prosthesis (13x3 cm) is inserted to ascertain adequate depth and width (left). The triangle form of the neoclitoris, from the penile glans, is incised (right).
Figure 3. When the penis has been degloved and the preputial envelope is dissected (left). Penile disassembly completed (right). A: Penile skin, B: Neoclitoral flap, C: Urethra with an inserted urinary catheter, D: Penile remnants.

Figure 4. The penile skin is inverted and invaginated to become the vaginal lining.

Figure 5. The clitoral flap and urethra are taken through the skin (left). After suturing of the neoclitoris as well as the urethra and labia majora, the vagina is packed with Vaseline gauze (right).
Figure 6. The final result approximately 12 months postoperatively. Perineal view (left) and frontal view (right) of two different patients. All photographs are published with a written consent from the patients.

2.2 SECONDARY SURGERY
The second surgical stage is performed approximately six months after the primary surgery. This delay is required to complete the healing and stretching of the invaginated tissues. A posterior commissure incision is made vertically in the posterior vaginal orifice to lower the commissure. Vaginoplasty to enhance the labia minora (inner labia) is performed when the patient has not yet acquired enough skin folds and an aesthetically-pleasing labia minora. By repositioning the additional skin at the posterior commissure towards the clitoral area, the labia minora is created. For clitoral hood creation, the adjacent skin is enveloped to cover the neoclitoris, thus narrowing the anterior commissure. No procedures to stretch or widen the neovaginal space are performed during the secondary surgery.

2.3 TERTIARY SURGERY
Despite thorough preparations and surgical technique, additional procedures are often needed. The reasons for revision include aesthetic improvements, reduction of the corpus spongiosa, fat grafting to the labia, dilation or revision, and repositioning of the urethral meatus. For unsuccessful primary vaginoplasties in which the penile skin has prolapsed, been damaged or when the vaginal depth is insufficient despite vaginal dilation, another surgical procedure may be required. These procedures include skin grafting and pedicled small or large bowel segments. 

Figure 6. The final result approximately 12 months postoperatively. Perineal view (left) and frontal view (right) of two different patients. All photographs are published with a written consent from the patients.
3 AIMS
The overarching aim of these studies was to evaluate the outcomes of gender confirming surgery (GCS) in transgender women. The primary aim was to investigate functional outcomes as a result of our specific surgical technique and to compare these results with published data from other GCS techniques. The secondary aim was to evaluate health-related quality of life before and after GCS. The specific aims were:

- To analyze demographics, minor and major complications, operation time and length of stay for patients undergoing MtF GCS (I).

- To investigate the vaginal depth of transgender women having undergone MtF GCS and compare the results with vaginal depth measurements of both trans and cis women from the current literature (II).

- To analyze the health-related quality of life of gender dysphoric patients with a validated standardized questionnaire, and to determine how the health-related quality of life is affected by MtF GCS (III).

- To measure the long term results with regards to sensitivity of the neoclitoris, orgasmic function and perceived satisfaction after MtF GCS (IV).
4 HYPOTHESES

Study I  Male-to-female GCS can be performed with a low rate of major complications. The rate of minor complications is comparable to other centers.

Study II  Performing MtF GCS as a two-step procedure with solely penile skin is not inferior for functional outcomes.

Study III  Health-related quality of life is poorer among transgender women prior to GCS compared to the general matched population, but is improved after GCS.

Study IV  Sensitivity of the neoclitoris after MtF GCS is sufficient for orgasmic function.

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5 PATIENTS
The four studies described here include patients who underwent MtF GCS at the Department of Plastic and Reconstructive Surgery, Karolinska University Hospital, from 2000 to 2015.

Study I
A total of 205 (n=205) primary MtF GCS procedures were performed over a 14-year period, from January 1st 2000 to December 31st 2013. All patients were included in the study, as no exclusion criteria were applied.

Study II
Eighty (n=80) patients who underwent MtF GCS vaginoplasty from January 1st 2000 to December 31st 2014 were measured for vaginal depth at the time of the secondary surgical procedure, at least six months after the primary operation.

Study III
All consecutive patients undergoing MtF CGS from January 1st 2003 to December 31st 2015 were prospectively asked to complete a health-related quality of life (QoL) questionnaire. A total of 190 (n=190) patients were included in the study, and no exclusion criteria were applied. A total of 146 patients completed the questionnaires preoperatively; 108 completed the questionnaire one year postoperatively, 64 at three years, and 43 at five years.

Study IV
Sixty-five patients who had undergone GCS at Karolinska University Hospital between January 1st 2011 and June 1st 2015 with a minimum follow-up time of one year and who were living in the Stockholm area were invited to participate in the study. A total of 22 patients (n=22) responded and were willing to cooperate. The remaining 43 patients did not respond to the invitation letter. No further contact with these patients was attempted by the researchers.

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6 METHODS

6.1 DEMOGRAPHICS, COMPLICATIONS AND OPERATION TIME (I)
A descriptive retrospective study was performed on a consecutive series of transgender women. Surgery was performed as described above. Solely penile skin was used for the vaginal lining when performing the penile inversion technique. To eliminate the risk of overlooking possible participants, two registries were used to identify patients. These were a centralized operation database (ORBIT®) and an internal quality registry including all transgender patients treated at our department. Data were retrieved and entered into Microsoft Excel (Microsoft Corp., Redmond, WA, USA), in which the analysis was performed. Standardized reporting guidelines was adhered to for cohort studies, using the STROBE guidelines [52].

6.2 VAGINAL DEPTH (II)
A prospective study was performed on consecutive patients who underwent a secondary GCS operation. A minimum of six months was allowed between the date of the primary surgery and the measurements performed at the secondary surgery. The vaginal depth of the patients was measured under general anesthesia in the lithotomy position at the end of the procedure using a semi-rigid silicone vaginal dilator (30 mm x 160 mm). The dilator was directed horizontally and allowed to bottom out in the neovaginal cavity, and a marker was then used to draw a line parallel to the position of the inner labia (Figure 7). The distance from the tip of the dilator to the drawn mark was recorded in the patient chart. Measurements were performed according to a written protocol and after a teaching session to assure a comparable measuring technique between surgeons. Measurements of neovaginal depth were compared to the literature regarding vaginal depth in biological women including when aroused or unaroused [12-14].

Figure 7. A semi-rigid 30-mm wide dilator is directed parallel to the operating table and allowed to bottom out in the neovagina (left). The dilator is marked at the position of the inner labia and the distance from tip to the mark is measured (right).
Data regarding patient age, height, weight, and circumcision status were collected. Body mass index (BMI) was calculated. Information on postoperative complications was retrospectively collected. Following the primary surgery, the patients were prescribed a postoperative dilation regimen. Self-reported compliance with this regimen was noted.

The study was approved by the Stockholm Ethical Board under approval authentication Dnr. 2015/2225-31.

6.3  HEALTH-RELATED QUALITY OF LIFE (III)
In this prospective questionnaire-based study, the Swedish version of the Short Form-36 Health Survey (SF-36) was distributed to the patients. The questionnaire measures QoL on eight domains. The included domains address both emotional and physical components, and are comprised of mental health, vitality, bodily pain, social functioning, role emotional, role physical, physical functioning and general health, as well as perceived health compared to one year previously [53]. The questionnaire was answered by patients prior to GCS, as well as one, three and five years postoperatively, here called the measure points. The results were analyzed for differences between measure points and were compared to scores from the general population. A conversion of the answers was made, using a standardized transformation protocol, into scores from 0 to 100, where 100 represented the highest possible QoL. A Likert scale from 1-5, where 1 represented good (“much better now”) and 5 represented poor (“much worse now”), is used for the answers on perceived health compared to one year earlier. The Swedish SF-36 questionnaire has previously been validated [54-56]. Informed consent was obtained from all participants.

The study was approved by the Stockholm Ethical Board under approval authentication Dnr. 2015/2225-31.

6.4 SENSATION AND FUNCTIONALITY OF THE NEOCLITORIS (IV)
In this cohort study, data was gathered from medical records regarding complications (bleeding, infection, wound dehiscence and rectal perforation) during the previous surgery. The patients answered the Body Image Scale for Transsexuals (BIS) questionnaire [57]. This questionnaire is used to evaluate body satisfaction for transgender individuals. It is comprised of 30 body domains, which are rated on a Likert scale (range 1-5), with the highest score being 1 (“very satisfied”), and 5 (“very dissatisfied”) being the lowest. In this preliminary report, clitoris characteristics alone were examined. The BIS scale results have been reported earlier, and have shown a high sensitivity in the transgender population [58-60].
Furthermore, we asked the patients to answer three questions: 1. Have you had an orgasm (Y/N)? 2. Do you have feelings of genital pain or discomfort (1-10 VAS scale)? 3. Are you satisfied with having gone through with GCS (1-5 Likert scale)? At an outpatient clinic setting, a sensitivity measurement was performed by a plastic surgeon or a specialized nurse. Tactile sensitivity measurements were performed on the neoclitoris with a kit of 20 monofilaments called the Touch Test™ Sensory Evaluators Semmes-Weinstein Von Frey Aesthesiometers (Stoelting Europe, Dublin, Ireland). These filaments provide a non-invasive evaluation of cutaneous sensation levels, providing results that are objective and repeatable [61]. The procedure for measuring tactile sensitivity of the neoclitoris with the Semmes-Weinstein filaments is described in [33]. The vibration test for vibratory thresholds was performed using a Bio-Thesiometer (Bio-medical Instrument Company, Newbury, Ohio, USA). Measurements were done in a standardized fashion with graded amplitudes (volts) and then converted and presented in micrometers (µm) as described by the manufacturer. The amplitude of the Bio-Thesiometer was gradually increased until vibration was felt. The amplitude was then increased by two volts before it was decreased and the patient was asked to state when they no longer felt the vibration. This was repeated three times and a mean of these measurements was documented. The devices are shown in Figure 8.

The study was approved by the Stockholm Ethical Board, under approval authentication Dnr. 2015/2225-31.

![Image of the Touch Test™ Sensory Evaluators and Bio-Thesiometer](image1.png)

**Figure 8.** The Touch Test™ Sensory Evaluators, Semmes-Weinstein Von Frey Aesthesiometers (right) and Bio-Thesiometer (left).
7 STATISTICAL ANALYSIS

In study I, descriptive data concerning participant demographics are presented as the number of cases and frequencies (n, %). Mean and median values are given, including the range of values. For the statistical analysis in study II, the mean vaginal depth and range were calculated for age category, BMI category, circumcision, postoperative complications and compliance with the dilation regime. For evaluation of the association between vaginal depth and the continuous covariates, Pearson’s correlation coefficient was determined. To estimate the effect of all the above mentioned variables on the primary outcome (vaginal depth), simple linear regression models and a multivariate regression model were used. Two-tailed p-values were calculated, with a significance level of 0.05.

In study III, the scores for each of the eight domains in the SF-36 were calculated for each individual and measure point, as described by the authors of the SF-36 [53]. Calculations on average scores with standard deviations and confidence intervals were performed. To analyze variations amid scores from different domains the one-way ANOVA test was used. A significant level of 0.05 was set and calculated with two-tailed p-values. For internal consistency the Cronbach’s alpha test was used.

In study IV, VAS scores that were presented with numbers (0-10) were used. Pearson’s and Spearman’s rho coefficients were used to assess the correlation between measured values and variables. The significant level was set at 0.05.

All calculations were performed using STATA version 13.1 (StataCorp 2013 Stata Statistical Software: Collage Station, TX, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

7 STATISTICAL ANALYSIS

In study I, descriptive data concerning participant demographics are presented as the number of cases and frequencies (n, %). Mean and median values are given, including the range of values. For the statistical analysis in study II, the mean vaginal depth and range were calculated for age category, BMI category, circumcision, postoperative complications and compliance with the dilation regime. For evaluation of the association between vaginal depth and the continuous covariates, Pearson’s correlation coefficient was determined. To estimate the effect of all the above mentioned variables on the primary outcome (vaginal depth), simple linear regression models and a multivariate regression model were used. Two-tailed p-values were calculated, with a significance level of 0.05.

In study III, the scores for each of the eight domains in the SF-36 were calculated for each individual and measure point, as described by the authors of the SF-36 [53]. Calculations on average scores with standard deviations and confidence intervals were performed. To analyze variations amid scores from different domains the one-way ANOVA test was used. A significant level of 0.05 was set and calculated with two-tailed p-values. For internal consistency the Cronbach’s alpha test was used.

In study IV, VAS scores that were presented with numbers (0-10) were used. Pearson’s and Spearman’s rho coefficients were used to assess the correlation between measured values and variables. The significant level was set at 0.05.

All calculations were performed using STATA version 13.1 (StataCorp 2013 Stata Statistical Software: Collage Station, TX, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA).
8 RESULTS

STUDY I

During the study period in study I, from January 1st 2000 to December 31st 2013, a total of 205 primary MtF GCs were performed. The average age of the participants was 35.5 years (median: 33.0 years); the youngest patient was 18 years and the oldest 76 years of age. Over 90% of the patients (n=188) had undergone the secondary surgical procedure. Thirteen percent required a tertiary operation in addition to the secondary surgery for reasons including scar revision, resection of the corpus spongiosa, meatoplasty, rupture of the suture line or additional opening of the posterior commissure. The incidence of short-term (<30 days) complications is shown in Table 1. A total of 27 patients (11%) required reoperation or treatment with heamostatic medication due to bleeding in the immediate postoperative period (0-7 days). The frequency of postoperative bleeding reduced during the latter half of the period. Wound infection requiring antibiotic treatment occurred in 20 patients (10%). A total of four patients (2%) were found to have wound dehiscence requiring re-suturing or conservative treatment by secondary healing. A rectovaginal fistula occurred in four patients (2%), and pulmonary embolism in two patients (1%). There were no cases of deep vein thrombosis in the lower limbs (0%), and mortality was nil (0%). Operation time was on average 197 min. However, the length of surgery steadily decreased from 200-250 minutes at the beginning of the study period to <120 min in the year 2013. When compared with previous publications, the complication rates observed here were similar in type and frequency to that of other centers (Table 2).

Table I. Demographics and short-term postoperative complications after primary MtF GCs.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All patients n=205 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>35.5 (18-76)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Secondary surgery</td>
<td>108 (92)</td>
</tr>
<tr>
<td>Tertiary surgery</td>
<td>27 (13)</td>
</tr>
<tr>
<td>Short-term complications</td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring re-operation</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Wound infection requiring antibiotic treatment</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Clitoral flap necrosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rectovaginal fistula</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Operation time and length of stay</td>
<td></td>
</tr>
<tr>
<td>Operation time in min, mean (range)</td>
<td>197 (82-403)</td>
</tr>
<tr>
<td>Length of stay in days, mean (range)</td>
<td>7 (3-33)</td>
</tr>
</tbody>
</table>
STUDY II

Eighty (80) patients were measured for vaginal depth in study II. All measurements were collected at least six months after the primary surgery, with a median of 44 months. There was no statistical difference between patients measured at 6-12 months after primary surgery compared to measurements collected 1-2 years after primary surgery (10.7 versus 10.5 cm; p = 0.808; confidence interval [CI] = 2.385351, 1.863782). Vaginal depth (Table 3 and Figure 9) was an average of 10.2 cm (median: 10.4 cm, range: 1-16 cm). One or more postoperative complications was experienced by 11 patients (13.7%), whereas 69 patients (86.3%) experienced no complications (Table 1). The majority of participants reported compliance with the dilation protocol (68 participants; 85.0%), 11 (13.8%) did not, and one participant (1.2%) did not report. There was no statistically significant association between vaginal depth and BMI (Pearson correlation coefficient: 0.007; p = 0.95) or age (Pearson correlation coefficient: 0.089; p = 0.43). The effect of different covariates on vaginal depth was analyzed using a multiple regression model. The multivariate analysis found that noncompliance with the dilation protocol and having experienced a postoperative complication was associated with the outcome (Table 4). However, neither circumcision nor age affected the eventual vaginal depth. There was no association between vaginal depth and BMI, neither as a continuous variable nor as a categorical variable.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative bleeding</td>
<td>11.0%</td>
<td>-</td>
<td>4.5%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>10.0%</td>
<td>4.0%</td>
<td>-</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>2.0%</td>
<td>2.6%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Clitoral flap necrosis</td>
<td>0.0%</td>
<td>2.0%</td>
<td>-</td>
</tr>
<tr>
<td>Rectovaginal fistula</td>
<td>2.0%</td>
<td>2.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1.0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

N/A

Table 2. Comparison of the results from study I regarding the short-term complications of MtF GCS to previously published studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative bleeding</td>
<td>11.0%</td>
<td>-</td>
<td>4.5%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>10.0%</td>
<td>4.0%</td>
<td>-</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>2.0%</td>
<td>2.6%</td>
<td>5.2%</td>
</tr>
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<td>0.0%</td>
<td>2.0%</td>
<td>-</td>
</tr>
<tr>
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<td>2.0%</td>
<td>2.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1.0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

N/A

Table 2. Comparison of the results from study I regarding the short-term complications of MtF GCS to previously published studies.
Table 3. Vaginal depth by covariate.

<table>
<thead>
<tr>
<th>Age, median (range), years</th>
<th>Study participants (n=80)</th>
<th>Mean vaginal depth (range), cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29, n (%)</td>
<td>39 (48.8)</td>
<td>9.9 (1.0-13.8)</td>
</tr>
<tr>
<td>30-39, n (%)</td>
<td>38 (47.5)</td>
<td>10.4 (2.9-16.0)</td>
</tr>
<tr>
<td>60-69, n (%)</td>
<td>3 (3.7)</td>
<td>11.2 (9.0-13.4)</td>
</tr>
<tr>
<td>Body mass index, median (range), kg/m²</td>
<td>23 (17.34)</td>
<td>9.3 (1.0-13.2)</td>
</tr>
<tr>
<td>&lt;19, n (%)</td>
<td>14 (17.5)</td>
<td>10.4 (2.9-16.0)</td>
</tr>
<tr>
<td>19-25, n (%)</td>
<td>39 (48.8)</td>
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</tr>
<tr>
<td>&gt;25, n (%)</td>
<td>27 (33.7)</td>
<td>11.2 (9.0-13.4)</td>
</tr>
<tr>
<td>Circumcised, n (%)</td>
<td>Yes</td>
<td>14 (17.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27 (33.7)</td>
</tr>
<tr>
<td>Complications after first surgery, n (%)</td>
<td>No</td>
<td>69 (86.3)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0.0)</td>
<td>6.0 (7.2-11.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (2.5)</td>
<td>8.7 (4.0-11.4)</td>
</tr>
<tr>
<td>Deep infection</td>
<td>2 (2.5)</td>
<td>8.9 (7.2-10.6)</td>
</tr>
<tr>
<td>Wound rupture</td>
<td>1 (1.2)</td>
<td>2.9 (NA)</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>1 (1.2)</td>
<td>12.8 (NA)</td>
</tr>
<tr>
<td>Compliance, n (%)</td>
<td>Yes</td>
<td>68 (85.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11 (13.8)</td>
</tr>
<tr>
<td>Missing value</td>
<td>1 (1.2)</td>
<td>8.0 (NA)</td>
</tr>
</tbody>
</table>

Figure 9. Distribution (Bell) curve of neovaginal depth measurements.

Table 3. Vaginal depth by covariate.

<table>
<thead>
<tr>
<th>Age, median (range), years</th>
<th>Study participants (n=80)</th>
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</tr>
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</tr>
<tr>
<td>60-69, n (%)</td>
<td>3 (3.7)</td>
<td>11.2 (9.0-13.4)</td>
</tr>
<tr>
<td>Body mass index, median (range), kg/m²</td>
<td>23 (17.34)</td>
<td>9.3 (1.0-13.2)</td>
</tr>
<tr>
<td>&lt;19, n (%)</td>
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</tr>
<tr>
<td>19-25, n (%)</td>
<td>39 (48.8)</td>
<td>10.4 (2.9-13.4)</td>
</tr>
<tr>
<td>&gt;25, n (%)</td>
<td>27 (33.7)</td>
<td>10.2 (4.0-16.0)</td>
</tr>
<tr>
<td>Circumcised, n (%)</td>
<td>Yes</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>73 (91.2)</td>
</tr>
<tr>
<td>Complications after first surgery, n (%)</td>
<td>No</td>
<td>69 (86.3)</td>
</tr>
<tr>
<td>No complication</td>
<td>69 (86.3)</td>
<td>10.5 (1.6-16.0)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6 (7.5)</td>
<td>8.7 (4.0-11.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Deep infection</td>
<td>1 (1.2)</td>
<td>6.0 (NA)</td>
</tr>
<tr>
<td>Wound rupture</td>
<td>2 (2.5)</td>
<td>8.9 (7.2-10.6)</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>1 (1.2)</td>
<td>2.9 (NA)</td>
</tr>
<tr>
<td>More than one complication</td>
<td>1 (1.2)</td>
<td>12.8 (NA)</td>
</tr>
<tr>
<td>Compliance, n (%)</td>
<td>Yes</td>
<td>68 (85.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11 (13.8)</td>
</tr>
<tr>
<td>Missing value</td>
<td>1 (1.2)</td>
<td>8.0 (NA)</td>
</tr>
</tbody>
</table>

Figure 9. Distribution (Bell) curve of neovaginal depth measurements.
A small number of studies have reported the vaginal depth of biological women. A magnetic resonance imaging study showed vaginal depth to be in the range of 4.1-9.5 cm, with a mean of 6.9 cm [62]. A study using molding casts measured the depth from 6.9-14.8 cm [63], and a study of women in unaroused versus aroused states showed means of 7.8 cm versus 11-12 cm, respectively [64]. The vaginal depth of trans women measured in our study was within this range for the abovementioned measurement modalities (Table 5).

Table 4. Estimates of coefficients from simple linear and multivariate regression.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Linear regression</th>
<th>Multivariate regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>Age category (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>30-59</td>
<td>0.45</td>
<td>0.46</td>
</tr>
<tr>
<td>60-69</td>
<td>1.29</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI category (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;19</td>
<td>-1.15</td>
<td>0.16</td>
</tr>
<tr>
<td>19-25</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>-2.11</td>
<td>0.75</td>
</tr>
<tr>
<td>Circumcised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-1.11</td>
<td>0.28</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complication</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>-1.74</td>
<td>0.10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Deep infection</td>
<td>-4.46</td>
<td>0.07</td>
</tr>
<tr>
<td>Wound rupture</td>
<td>-1.56</td>
<td>0.37</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>-7.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;1 complication</td>
<td>2.34</td>
<td>0.34</td>
</tr>
<tr>
<td>Any complication</td>
<td>-2.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-4.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Missing value</td>
<td>-</td>
<td>NA</td>
</tr>
</tbody>
</table>

A small number of studies have reported the vaginal depth of biological women. A magnetic resonance imaging study showed vaginal depth to be in the range of 4.1-9.5 cm, with a mean of 6.9 cm [62]. A study using molding casts measured the depth from 6.9-14.8 cm [63], and a study of women in unaroused versus aroused states showed means of 7.8 cm versus 11-12 cm, respectively [64]. The vaginal depth of trans women measured in our study was within this range for the abovementioned measurement modalities (Table 5).
The mean scores of the eight dimensions at times 0, 1, 3 and 5 are presented in Table 7. Internal consistency was high (Cronbach’s alpha: 0.86).

Table 5. Vaginal depth, comparison to biological vagina.

<table>
<thead>
<tr>
<th>Health domains</th>
<th>Year 0 (study pop)</th>
<th>General population (women, all age groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>95 % CI</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Mental health</td>
<td>66.6 (24.2)</td>
<td>62.7-70.6</td>
</tr>
<tr>
<td></td>
<td>79.6 (10.4)</td>
<td>79.0-80.2</td>
</tr>
<tr>
<td>Vitality</td>
<td>58.8 (25.3)</td>
<td>54.6-62.9</td>
</tr>
<tr>
<td></td>
<td>66.7 (13.2)</td>
<td>66.0-67.4</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>80.1 (25.3)</td>
<td>75.9-84.3</td>
</tr>
<tr>
<td></td>
<td>72.7 (12.5)</td>
<td>71.9-73.4</td>
</tr>
<tr>
<td>Social functioning</td>
<td>73.7 (27.0)</td>
<td>69.1-78.2</td>
</tr>
<tr>
<td></td>
<td>87.5 (20.8)</td>
<td>86.9-88.1</td>
</tr>
<tr>
<td>Role emotional</td>
<td>69.5 (19.7)</td>
<td>62.9-76.0</td>
</tr>
<tr>
<td></td>
<td>84.0 (30.9)</td>
<td>83.1-85.0</td>
</tr>
<tr>
<td>Role physical</td>
<td>82.5 (30.4)</td>
<td>77.5-87.5</td>
</tr>
<tr>
<td></td>
<td>81.6 (33.1)</td>
<td>80.6-82.6</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>91.2 (13.7)</td>
<td>89.0-93.4</td>
</tr>
<tr>
<td></td>
<td>86.2 (20.4)</td>
<td>85.6-86.8</td>
</tr>
<tr>
<td>General health</td>
<td>52.0 (10.4)</td>
<td>50.3-53.7</td>
</tr>
<tr>
<td></td>
<td>75.1 (22.7)</td>
<td>74.5-75.8</td>
</tr>
</tbody>
</table>

STUDY III
A total of 190 patients completed the SF-36 on at least two instances. A total of 17 patients completed the questionnaire for all four measure points. Preoperatively, 146 patients completed the SF-36: 108 at one year, 64 at three years and 43 at five years postoperatively. Reasons for loss to follow-up were: moved from Sweden, moved house without disclosing residence, not registered in the Swedish residential registry or deceased. Average age was 36 years (19-76 years). QoL of transgender women was significantly lower in five dimensions; mental health, vitality, social functioning, role emotional and general health when compared to the general population (Table 6). Higher scores were in the domains of bodily pain and physical functioning compared to the general population.

The mean scores of the eight dimensions at times 0, 1, 3 and 5 are presented in Table 7. Internal consistency was high (Cronbach’s alpha: 0.86).
We observed a trend towards higher scores on the SF-36 one year postoperatively compared to the preoperative scores. The one year score was also the highest documented of all measure points. There was also a trend towards lower scores five years postoperatively compared to preoperatively. These trends were not statistically significant (p > 0.05).

In the SF-36 patients compare their present perceived health to that of one year earlier. Average scores for years 0, 1, 3 and 5 were 2.4, 2.1, 2.8 and 2.8, respectively. There was a significant improvement in scores between 0 and 1 year (p < 0.05). Results for years 3 and 5 were significantly poorer when compared to year 1 (p < 0.0001), but not to year 0. When analyzing only those who completed the questionnaire for all measure points we saw no significant difference from that of all study participants.

Table 7. Average SF-36 scores for all individuals on all five measure points in the study.

<table>
<thead>
<tr>
<th></th>
<th>0 years Mean (SD)</th>
<th>0 years 95% CI</th>
<th>1 years Mean (SD)</th>
<th>1 years 95% CI</th>
<th>3 years Mean (SD)</th>
<th>3 years 95% CI</th>
<th>5 years Mean (SD)</th>
<th>5 years 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health</td>
<td>66.6 (24.2)</td>
<td>62.7-70.6</td>
<td>70.1 (24.0)</td>
<td>65.5-74.6</td>
<td>67.7 (25.3)</td>
<td>61.4-73.9</td>
<td>66.1 (26.6)</td>
<td>58.2-74.1</td>
</tr>
<tr>
<td>Vitality</td>
<td>58.8 (25.3)</td>
<td>54.6-62.9</td>
<td>61.1 (25.5)</td>
<td>56.2-65.9</td>
<td>59.2 (23.8)</td>
<td>53.3-65.0</td>
<td>57.3 (26.6)</td>
<td>49.4-65.3</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>80.1 (25.3)</td>
<td>75.9-84.3</td>
<td>82.1 (24.4)</td>
<td>77.4-86.7</td>
<td>78.6 (28.0)</td>
<td>71.6-85.6</td>
<td>72.5 (26.5)</td>
<td>64.5-80.4</td>
</tr>
<tr>
<td>Social functioning</td>
<td>73.7 (27.0)</td>
<td>69.1-78.2</td>
<td>77.5 (27.7)</td>
<td>72.2-82.8</td>
<td>73.8 (28.4)</td>
<td>66.8-80.8</td>
<td>69.8 (29.4)</td>
<td>60.8-78.9</td>
</tr>
<tr>
<td>Role emotional</td>
<td>69.5 (39.7)</td>
<td>62.9-76.0</td>
<td>69.1 (41.2)</td>
<td>61.3-76.9</td>
<td>65.1 (41.7)</td>
<td>54.6-75.4</td>
<td>59.7 (44.0)</td>
<td>46.5-72.9</td>
</tr>
<tr>
<td>Role physical</td>
<td>82.5 (30.4)</td>
<td>77.5-87.5</td>
<td>82.9 (32.7)</td>
<td>78.7-89.2</td>
<td>79.3 (33.5)</td>
<td>71.1-87.5</td>
<td>70.9 (42.2)</td>
<td>58.3-83.6</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>91.2 (13.7)</td>
<td>89.0-93.4</td>
<td>92.4 (13.9)</td>
<td>89.8-93.0</td>
<td>89.7 (17.6)</td>
<td>85.4-94.1</td>
<td>91.5 (11.8)</td>
<td>88.0-95.1</td>
</tr>
<tr>
<td>General health</td>
<td>52.0 (10.4)</td>
<td>50.3-53.7</td>
<td>51.9 (12.2)</td>
<td>49.6-54.2</td>
<td>50.0 (12.1)</td>
<td>47.0-53.0</td>
<td>48.1 (12.6)</td>
<td>44.2-51.9</td>
</tr>
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</table>

We observed a trend towards higher scores on the SF-36 one year postoperatively compared to the preoperative scores. The one year score was also the highest documented of all measure points. There was also a trend towards lower scores five years postoperatively compared to preoperatively. These trends were not statistically significant (p > 0.05).

In the SF-36 patients compare their present perceived health to that of one year earlier. Average scores for years 0, 1, 3 and 5 were 2.4, 2.1, 2.8 and 2.8, respectively. There was a significant improvement in scores between 0 and 1 year (p < 0.05). Results for years 3 and 5 were significantly poorer when compared to year 1 (p < 0.0001), but not to year 0. When analyzing only those who completed the questionnaire for all measure points we saw no significant difference from that of all study participants.
STUDY IV

The average follow-up time for the patients studied was 37 months (range: 12-63 months) after initial GCS. The median age of the patients was 45 years (range: 23-63 years). Of the 22 patients, only one had been circumcised in childhood. The average pressure threshold for the neoclitoris was 12.5 g/mm² (range: 1.4-29.2 g/mm²). The average vibratory threshold was 0.3 µm (range: 0.07-0.74 µm). The circumcised patient had a better than average vibratory threshold (0.25 µm), but the lowest registered score on pressure thresholds (29.19 g/mm²). Four patients had postoperative bleeding which was managed with additional dressing and haemostatic medicine (tranexamic acid or desmopressin) and two patients suffered from wound dehiscence. In a study published by Selvaggi et al. (2007) [33], clitoral sensitivity among trans women was measured using the same methods and devices as described here. Our results are in line with their findings on pressure and vibratory sensation (11.1 g/mm² and 0.5 µm, respectively). A further relevant comparison (Table 8) may be that of the un-operated male glans penis, which was reported by Gilbert et al. (1988) [65] to be 18.5 g/mm² and 0.2 µm, respectively. 

Table 8. Comparison of pressure and vibratory thresholds between published studies.

<table>
<thead>
<tr>
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</tr>
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<td>Pressure thresholds (g/mm²)</td>
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<td>Vibratory thresholds (µm)</td>
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<td>0.5 (0.04-9)</td>
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Patients were asked about having had an orgasm, pain and general satisfaction of having undergone GCS. Nineteen patients reported the ability to reach orgasm (86%), one was not able to reach orgasm (4.5%) and two had not attempted to reach orgasm (9%). The visual analogue scale (VAS, 0-10) was used to report genital pain or discomfort. Nineteen patients (86%) reported no pain (VAS: 0), and three patients (14%) reported pain at low levels of discomfort (VAS: 2, 3 and 4). No difference was found between these three groups with regards to the objective sensitivity testing for any modality. When asked to indicate satisfaction with having undergone GCS on a scale from 1-5, where 1 represented the best score (“very satisfied”) and 5 the worst score (“very dissatisfied”), 19 patients answered that they were very satisfied (score: 1) or satisfied (score: 2). Three patients were neither satisfied nor dissatisfied (score: 3). The average score was 1.5. When Pearson and Spearman’s tests were used we found no or week statistical correlation between sensitivity of the clitoris (both pressure and vibratory

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thresholds) and the answers on the clitoris aspect in BIS, orgasmic function, having had complication or satisfaction with surgery.
9 DISCUSSION

In study I, we present our complete records and long-term experience of patients who underwent GCS. This should be a reliable representation of the short-term outcome. When compared with previous publications (Table 2), our complications were similar in type and frequency to that of other centers [27, 28]. However, the incidence of bleeding and infection was higher. One reason for this may be that we used a liberal inclusion criteria for these groups. For the bleeding group we included all patients with bleeding treated with hemostatic medicine (tranexamic acid or desmopressin) in addition to those who underwent a re-operation for bleeding. We observed a decrease in the frequency of postoperative bleeding during the study period. Infections were more frequent in comparison to that reported in other publications. We defined infection as the “use of antibiotics other than perioperative prophylaxis.” The vast majority of the patients with infection had minor suture-line infections or urinary tract infections. Wound dehiscence was rare (2%). Rectovaginal fistula has been reported to occur at an incidence of 1-3% [25, 27, 66] and occurred in 4 patients (2%) in our data. The incidence of thrombotic events was rare. Two cases of pulmonary embolism (PE) occurred early in the study period that led to the revision of the antithrombotic prophylaxis. Thereafter, no cases of PE were observed. Another factor involved in protection against a thrombotic event was the absence of hormonal therapy four weeks preoperatively and two weeks postoperatively. Another risk factor for thrombotic events is a prolonged lithotomy position during surgery, which is also a risk factor for compartment syndrome in the lower leg [67, 68]. In our investigation, we saw no cases of deep vein thrombosis or compartment syndrome, possibly due to the short operating time, of which we observed a dramatic reduction during the study period. The main goals of MfF-GCS are the creation of a functional neovaginal vault, a sensitive neoclitoris, and an ability to void urine [26]. The aesthetic outcome has received increased focus by both patients and surgeons during recent years [3]. Our technique uses a second operation for the reconstruction of the labia minora, clitoral hood and minor scar revision. This two-stage strategy may be advantageous in the challenge to succeed in attaining an aesthetically pleasing outcome.

Vaginal depth is the one of the most common areas of discussion among patients and surgeons within the field of GCS. In study II, we measured the vaginal depth of a large patient cohort. A comparison of the vaginal measurements attained here with those of biological women showed that our surgical technique yields long-term results well within the range of the latter [62, 63]. This indicates that penetrative sexual intercourse is anatomically possible. In a recent study by Buncamper et al. (2015), transsexual women were operated upon using a similar penile skin

29
vaginoplasty technique. The results showed general satisfaction with the functional and aesthetic outcomes as determined by questionnaires [69], which is in concordance with our experience.

The technique of using solely penile skin brings major benefits, as the penile skin is supple, non-hair bearing [69, 70] and leaves no intravaginal scarring or donor site morbidity. Only four patients were excluded from the study because they had limited availability of penile skin and hence were operated upon using other techniques. A vaginal dilation regime is prescribed to the patients postoperatively (20 minutes, two to three times daily). Adhering to this regime is crucial, as non-compliant patients had a significantly reduced average vaginal depth. Empirically, dilation has a limited effect on increasing depth, but is necessary to prevent reduction of the vaginal space or in the worst case even collapse and prolapse [71, 72]. When compared with other techniques, e.g., penoscrotal vaginoplasty, the dilation regimes are similar [73]. The use of pedicled intestinal grafts [26, 74] may limit the need for postoperative dilation, but has possible drawbacks such as colitis [75] and an increased risk for intra-abdominal complications. Increased BMI and age did not negatively affect the outcome. This indicates that this technique is also suitable for heavier and older patients. Peri- or postoperative complications were associated with reduced neovaginal depth. However, because this was a small group of patients of which two patients sustained major complications (rectal injury/deep bleeding), interpreting the effects of less serious complications is difficult.

Regarding quality of life (QoL) before and after GCS, there is a paucity of prospective studies containing a large number of participants, a long follow-up time and comparison groups [23]. Study III describes a large, prospective QoL, questionnaire study of a cohort of 190 transgender women. Compared to the general population, these patients reported a lower QoL. GCS led to an initial trend towards an improved QoL, which decreased with time. This fact, namely that QoL shows a trend towards decreasing over time, warrants attention being drawn towards psychological support and the prospective long-term follow-up of transgender patients after GCS. Reasons for this decline may include disappointment with the surgical results, or that those who were dissatisfied or suffered complications after GCS were those who completed the follow-up questionnaires. General QoL declines with time, which may be a possible explanation why we also observed this decline in our material [53]. A study by Weyers et al. (2008) [21], using a similar questionnaire, reported higher QoL scores in psychological and social domains after GCS and a lower QoL in physical health domains. When the studies are compared, the subjects in our material reported improvement in almost all dimensions at the one-year postoperative timepoint; however, this improvement decreased over the measure
points. Our findings of a lower QoL in transgender women compared to the general population of women is the same observation found in a number of previous studies [17, 19, 76]. Our results, that lower QoL reported by transgender women compared to the general population, confirm the vulnerability of transgender patients, and emphasize the necessity of suitable care and treatment.

The sensitivity of the neoclitoris and its patient-reported function were studied in study IV. When our results are compared to results of a previous study by Selvaggi et al. (2007) [33] using the same instruments for measurement, the results are similar. A study by Gilbert et al. (1988) [65] regarding the glans penis also had similar results. Our results regarding the magnitude of sensitivity are thus comparable, indicating that the smaller surface area used for the neoclitoris compared to the entire male glans does not largely affect sensory thresholds upon stimuli. Objective measurements on sensitivity were combined with patient-reported outcomes. However, the manuscript of study IV only includes a preliminary report of the clitoral characteristic from the BIS questionnaire. Observing a non-correlation between the clitoris aspect of the BIS questionnaire and pressure or vibratory thresholds may indicate that the sensitivity of the neoclitoris is good, and that some paresthesia of the reconstructed organ does not limit the orgasmic function. For patient reports regarding I) having experienced orgasm, II) satisfaction with having undergone surgery and III) the occurrence of genital pain or discomfort, no overall differences were found when correlating with the objective testing results for any answer. The responses to all three questions were favorable by the vast majority of patients. Eighty-six percent of patients reported having had orgasm, and 86% reported experiencing no pain. Complications (e.g., bleeding or wound dehiscence) after GCS may be a possible risk factor for decreased sensitivity. However, the patients who sustained complications did not show reduced sensitivity of the neoclitoris. Although this is a rather small cohort, the results indicate that GCS using the pedicled glans penis for neoclitortial reconstruction is a reliable method for attaining long-term sexual sensitivity and orgasmic function.

9.1 LIMITATIONS
A limitation of study I is its retrospective nature, as a prospective study design would have increased the reliability of the results. In study II, most of the measurements were performed by two surgeons, which may have affected the results despite a detailed measuring protocol and training period to assure inter-rater reliability. The width of the dilator may have affected measurements, which is an inherent shortcoming of a study protocol as described here. We did not, however, experience that the 30 mm-wide dilator was difficult to use in any patient.
Although we do not know the percentage of patients who have had penetrative intercourse, our results indicate that it should indeed be anatomically possible.

The main limitation of study III was the incomplete follow-up. Further limitations includes not being able to adjust for factors such as comorbidities, other medical treatments and psychosocial standing. However, the major finding of the study, that transgender women have poorer QoL, compared to the general population, is true regardless of comorbidities and sociodemographic factors, as the SF-36 standard populations do not take such factors into account.

In study IV, only 35% of the patients invited were willing to participate in the study. We therefore cannot determine whether the respondents were representative of the entire group.

9.2 FUTURE PERSPECTIVES AND RESEARCH

Studies in this surgical field are heterogeneous regarding surgical techniques and outcome measures, and some do not use standardized research tools. Therefore, a gold standard has not been established regarding the techniques used for vaginoplasty in MtF GCS.

The ideal method to differentiate between the different techniques available for vaginoplasty would be a multicenter randomized controlled study with validated standardized questionnaires and a lengthy follow-up period.

Autologous tissue engineering has shown promising results in vaginoplasty, where long-term follow-up showed a low rate of complications [77]. This field is relatively unexplored and requires further attention.

Thorough long-term follow up of QoL, body image, sexual function and psychological support after GCS is important. The best probable outcomes will probably come from centers with extensive experience in treating transgender patients. Managing transgender patients should be localized to a few specialized centers in countries with small populations, such as Sweden.

The patient’s perspective regarding the outcome of surgical procedures has received increased focus in recent years. Studying patient-reported outcome measures will become increasingly important in future research, to provide treating doctors with feedback on different aspects of GCS.

An emphasis on quality research is crucial to making the treatments for gender dysphoria evidence based.

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10 CONCLUSIONS

MtF GCS can be performed with a low incidence of major complications. Our results are similar with regards to complication rate when compared to publications from other large centers performing GCS. Our data indicate that increasing surgical experience leads to shorter operating times and a lower number of complications. This suggests that GCS should be performed at a restricted number of centers, so that surgical experience and volume may be optimized.

Using solely penile skin to create the vaginal lining in MtF GCS is adequate for most patients. The benefits include less intravaginal hair-bearing skin and no intravaginal scars. Adhering to a dilation protocol is crucial for sustained vaginal depth. Complications during surgery such as major bleeding or rectal injury can result in reduced vaginal depth; BMI and age do not significantly affect outcomes.

When compared to the general population, transgender women report a lower quality of life (QoL). Surgical treatment has the possibility to relieve gender dysphoria and thereby raise QoL. However, this improvement shows a trend to decline over time. This confirms the vulnerability of the transgender population and emphasizes the need for suitable care both before and after GCS.

The neoclitoris has a protective tactile sensation, and can provide erogenous sensitivity and the ability to reach orgasm. In general, the vast majority of patients who undergo MtF GCS are satisfied.
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