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Nerve sparing feminizing genitoplasty with corporal septum excision in non-classic congenital adrenal hyperplasia

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Ethics Committee Approval
Ethical committee approval was obtained from Istanbul Medipol University, Faculty of Medicine Ethical Committee (Aproval number: 36423-11.08.2018).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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Abstract

Background/Aim: Non-classic congenital adrenal hyperplasia (CAH) is a milder form of CAH. The CYP21A2 gene is involved in the etiopathogenesis of both severe (classic) and mild (non-classic) form CAH, however, genetic mutations in non-classic CAH result in less impairment of 21-hydroxylase activity. Therefore, as in classic CAH, patients with non-classical CAH have no signs and symptoms of cortisol deficiency. Instead, there may be signs of hyperandrogenism that can appear later in childhood or in early adulthood. Due to excess androgenic effect on clitoris, labia minora, majora and the vagina, feminizing genitoplasty should be performed to make gender identities consistent and reshape the proper genital anatomy for sexual intercourse. However, there are few studies and controversy on feminizing genitoplasty procedures in adulthood. In this study, we aimed to design a new procedure to spare the nerves of the clitoris as well as the clitoral body, along with the cavernous tissue.
Methods: This is a case series of nine patients with a mean age of 24.8 years diagnosed with non-classic CAH who underwent feminizing genitoplasty, in which nerve-sparing clitoroplasty was performed with corporal septum excision by ventral approach. Initially, diagnostic cystoscopy was performed to detect the level of vaginal confluence into the urogenital sinus. The enlarged clitoris was degloved from 10 mm proximal to the glans up to the symphysis pubis. Corporal septum was excised from the ventral part of the clitoris up to the bifurcation of crura. Neurovascular bundle was preserved completely dorsally, and the clitoris was folded over itself and fixed at the level of crural bifurcation at 3 and 9 o'clock positions. Degloved clitoral preputium was used as Byars' flaps for labiaplasty. A perineal inverted U incision was made and the vaginal introitus was enlarged with this flap. Female Genital Image Scale (FGIS) was used in the assessment of patients' postoperative genital self-image.
Results: Feminizing genitoplasty (nerve-sparing clitoroplasty with corporal septum excision, labiaplasty and perineal flap vaginoplasty) was performed in nine patients diagnosed with non-classic CAH. The mean operation time was 112 minutes with a range of 90-140 minutes. Urogenital sinus mobilization was not performed as the vaginal confluence into urogenital sinus was low in cystoscopy. Patients were re-assessed at 1 month, 3 months and 6 months postoperatively. FGIS scores showed that four patients were "very satisfied," one patient was "satisfied," 2 patients were "moderately satisfied", and one patient was "dissatisfied." The maximum follow-up was 2 years with no recorded short or long-term complications.
Conclusion: Nerve sparing clitoroplasty with corporal septum excision is a good option with satisfactory long-term results for non-classic CAH patients. However, we need many more comparative studies to decide the gold standard method for optimal physiologic and cosmetic outcomes in CAH patients.

Keywords: Feminizing genitoplasty, Congenital adrenal hyperplasia, Clitoroplasty

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Introduction

Congenital adrenal hyperplasia (CAH) is the most common sexual development disorder of individuals with 46XX genotype [1]. The incidence of CAH is one in 15,000 newborns [2]. A number of enzymatic defects in the production of cortisol cause a shunting of cortisol precursors to an alternate metabolic pathway, which results in an excess production of adrenal androgens (i.e., DHEA, androstenedione, and testosterone). 21-hydroxylase deficiency is the most common enzymatic defect, and a wide array of clinical features can be observed according to the level of impairment in cortisol and aldosterone biosynthesis [3]. There are three clinical phenotypes as follows: Classic salt-wasting (most severe), classic non-salt-wasting (simple-virilizing), or non-classic (mild or late-onset). Non-classic CAH is a milder form of the disease**.**

There is a close relationship between genotypic CYP21A2 mutations and phenotype [4]. However, genetic mutations associated with non-classical CAH result in less impairment of 21-hydroxylase activity. In the most severe form, concomitant aldosterone deficiency leads to salt wasting, while patients with non-classic CAH do not have cortisol deficiency. They have signs and symptoms of hyperandrogenism that are seen later in childhood or early adulthood. Although it is a milder form of the disease, they cannot have sexual intercourse without a feminizing genitoplasty procedure. Hirsutism, clitoromegaly, voice thickening, masculine muscle structure are other important problems of non-classic CAH female patients. The main aim of treatment in female patients with mild or non-classic CAH is controlling excess androgen and transforming its virilizing effect to feminizing. However, the surgical method for feminizing genitoplasty is controversial. We aimed to share our experience on nerve sparing feminizing genitoplasty with corporal septum excision in non-classic CAH patients.

Materials and methods

We retrospectively reviewed the files of nine female patients diagnosed with mild CAH who underwent feminizing genitoplasty at two university hospitals between 2012-2020. All patients were married with a mean age of 24.8 years (range: 21 - 32 years) and presented with enlarged clitoris with inability to have sexual intercourse. Physical exam revealed clitoromegaly, vaginal stenosis and increased perianal distance (Figure 1). The uterus and ovaries were normal in pelvic ultrasound. Chromosome analysis was performed in all patients and resulted as 46XX. Their medical therapy was planned by an endocrinologist. They did not start cortisol replacement, and instead, Spironolactone, an aldosterone antagonist, was administered for its anti-androgenic effect. Ethinylestradiol and cyproterone acetate combination was added to medical therapy to speed up the regression of the virilizing signs and symptoms. Ethical committee approval was obtained from Istanbul Medipol University, Faculty of Medicine Ethical Committee (Approval number: 36423-11.08.2018). All patients read and signed the informed consent forms.

Surgical technique

All patients were operated under general anesthesia and the procedure began with diagnostic cystoscopy to exclude high confluence of urogenital sinus. Then, a 14F urinary catheter was inserted into the bladder, and the perianal trigone was marked with a sterile pencil (Figure 2a). A stay suture was placed for traction at the 12 o'clock position on the glans (Figure 2b). A circumcisional incision was made 10 mm proximal to the glans dorsally and 2 mm ventrally all around the shaft. The clitoris was degloved from 10 mm proximal to the corona up to the symphysis pubis (Figure 2c). Corporal septum was excised ventrally up to the bifurcation of crura (Figure 2d). Neurovascular bundle was preserved completely dorsally. The clitoris was folded over itself and fixed at the level of crural bifurcation at 3 and 9 o'clock positions (Figure 2e). Degloved clitoral preputium was used as Byars' flaps for labia minora reconstruction (Figure 2f). Then, a perineal inverted U incision was made, with which the vaginal introitus was enlarged (Figure 2g). A vaginal tamponade with estrogen cream was inserted into the vagina (Figure 2h).

Figure 1: Preoperative appearance of the external genitalia of a non-classic CAH patient

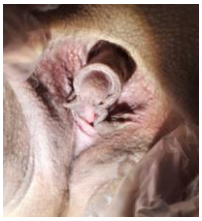
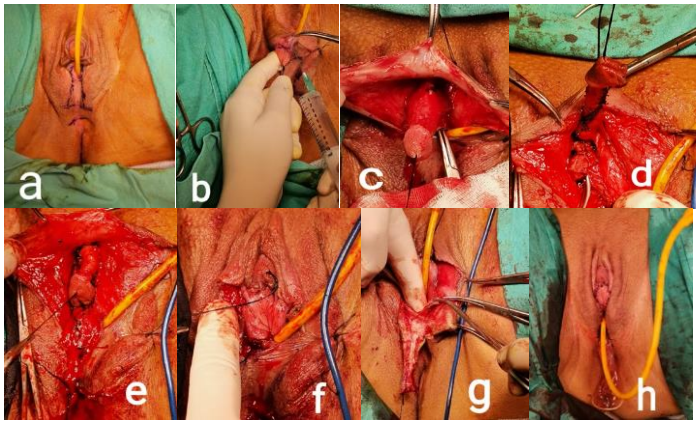


Figure 2: Step by step nerve sparing feminizing genitoplasty with corporal septum excision procedure



Patients were hospitalized for two nights. Control examinations were performed at one week, six weeks and three months postoperatively. Vaginal mold tamponade and urethral catheter were removed at the control examination at the first postoperative week. Female Genital Image Scale (FGIS), including 12 items, was used for the patients to rate their genital satisfaction along a five-point Likert-type scale from 1 = "Very satisfied" to 5 = "Very dissatisfied" at the control examination at three months postoperatively [5].

Results

Feminizing genitoplasty (nerve sparing clitoroplasty with corporal septum excision, labiaplasty and perineal flap vaginoplasty) was performed in nine patients diagnosed with non-classic CAH. The mean operation time was 112 minutes with a range of 90-140 minutes. Urogenital sinus mobilization was not performed as the vaginal confluence into urogenital sinus was low at cystoscopy. Preoperative mean clitoral size was 7.2 cm (6.8 cm-8.8 cm), which decreased to a mean of 2.3 cm (1.2 cm-2.6 cm) postoperatively. All patients started sexual

activity 8 weeks later. FGIS scale scores obtained three months later showed that four patients were “very satisfied,” one patient was “satisfied,” two patients were “moderately satisfied,” and one patient was “dissatisfied” (Table 1). The mean follow-up period was 13 months with a range of 8 to 26 months. There were no significant short- or long-term complications.

Table 1: Patients’ FGIS scale scores

FGIS scale	n (%)
1-Very Satisfied	4(44.4)
2- Satisfied	1(11.1)
3-Moderate	2(22.2)
4-Dissatisfied	1(11.2)
5-Very Dissatisfied	1(11.1)

Discussion

Females with classic CAH are usually diagnosed at birth with noticeable penis-like appearance of the clitoris. In-utero exposure of excess fetal adrenal androgens lead to clitoral enlargement. On the other hand, females with non-classic CAH are not diagnosed so early. They are usually diagnosed later in childhood or early adulthood. Most cases are referred to the physicians due to inability to have sexual intercourse when they get married. Their internal genitalia are anatomically female, and they have regular or irregular menstrual cycles. Their phenotype is influenced by the severity of the CYP21A2 mutations and 21-hydroxylase enzyme defect, leading to virilization of the external genitalia at varying levels. Physicians should be informed about the other conditions that can cause enlargement of the clitoris, such as exogenous in-utero androgen exposure due to the pregnant mother suffering from masculinizing tumors such as arrhenoblastoma [Ovarian Sertoli-Leydig cell tumors (SLCTs)] of the ovary or exogenous topical androgen use [6-8]. Some reports state that clitoral enlargement can be secondary to neurofibromatosis [9]. Another important condition causing idiopathic clitoromegaly in females is prematurity [10].

The main purpose of feminizing genitoplasty procedure is providing a proper width vaginal introitus and decreasing clitoral size to obtain a feminine genital appearance. It is documented in some studies that the clitoral length may vary according to ethnicity, like penile length [11]. However, the normal range for each ethnic race is not determined precisely. Considering our country, the mean clitoral length of Turkish newborns was reported as 4.93 (1.61) mm in a research [12]. Our study populations’ preoperative mean clitoral length was 7.2 cm. The clitoris is attached by the suspensory ligament to the front of the symphysis pubis]. However, the size of free part varies considerably as it has cavernous tissue [13]. For example, the clitoral body is 1–3 cm long in the flaccid state [14]. A physician first suspects clitoromegaly on physical examination. It is currently defined as a clitoris longer than 1 cm in newborns [15]. Parity can also affect clitoral size but age, body mass index and oral contraceptive use do not [16]. The most important step while reducing clitoral size is to preserve the neurovascular bundle of the clitoris. Poppas et al. described the nerve sparing ventral clitoroplasty procedure [17]. They examined the nerves in situ using optical coherence technology**.** Many women who underwent infant genitoplasty in 1980s were mutilated because the importance of clitoral sensation was not known at the time [18]. Old surgical techniques are no longer used, while nerve-sparing clitoroplasty has become widely adopted since the 2000s. The infants operated with old techniques report decreased sensation of the clitoris, and some of them are anorgasmic [19]. One study found the rate of anorgasmia to be as high as 40% [20].

Extensive clitoral resection should not be performed. A clear understanding of clitoral anatomy is important for surgical reconstruction. As in the human penis, nerves in the clitoris form an extensive network around the tunica of the dorsal corporeal body. The nerve-free zone is found in the midline, at 12 o'clock position [21]. For this reason, operation starts with a traction suture placed on clitoral glans at 12 o’clock. Nowadays, more effort is made to preserve nerves, which we also hoped to achieve with dorsal nerve-sparing clitoroplasty. In addition, we did not completely remove the corpus cavernosum ventrally. The human clitoris has two corporeal bodies that are smaller but analogous with the penis. A fibrous midline septum exists on the ventral aspect and extends approximately halfway into the glans [21]. We tried to excise this septum to be able to fold the clitoris over itself, hence decreasing clitoral size while preserving the corporal body.

To the best of our knowledge, this is the first study reporting dorsal nerve-sparing clitoroplasty performed on non-classic CAH adult females, because most studies are conducted on classic CAH during the newborn or childhood period. We could assess patients’ postoperative cosmetic and functional outcomes with FGIS more clearly as they were all sexually active adults. There were two major limitations to this study. One was the small sample size and the other, lack of a control group.

Conclusion

Nerve sparing clitoroplasty with corporal septum excision may be a good option with satisfactory long-term results for non-classic CAH patients. However, we need more comparative, multicenter studies to determine a gold standard method for achieving the optimal physiologic and cosmetic outcome in CAH patients. In the future, we hope to improve surgical techniques to preserve the corporal body in addition to nerve bundle.

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