Mini-Review

Research on Quality of Life in Female Patients with Congenital Adrenal Hyperplasia and Issues in Developing Nations

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A B S T R A C T

Congenital adrenal hyperplasia (CAH) is the commonest cause of ambiguous genitalia for female newborns and is one of the conditions under the umbrella term of "Disorders of Sex Development" (DSD). Management of these patients require multidisciplinary collaboration and is challenging because there are many aspects of care, such as the most appropriate timing and extent of feminizing surgery required and attention to psychosexual, psychological, and reproductive issues, which still require attention and reconsideration, even in developed nations. In developing nations, however, additional challenges prevail: poverty, lack of education, lack of easily accessible and affordable medical care, traditional beliefs on intersex, religious, and cultural issues, as well as poor community support. There is a paucity of long-term outcome studies on DSD and CAH to inform on best management to achieve optimal outcome. In a survey conducted on 16 patients with CAH and their parents in a Malaysian tertiary center, 31.3% of patients stated poor knowledge of their condition, and 37.5% did not realize that their medications were required for life. This review on the research done on quality of life (QOL) of female patients with CAH aims: to discuss factors affecting QOL of female patients with CAH, especially in the developing population; to summarize the extant literature on the quality of life outcomes of female patients with CAH; and to offer recommendations to improve QOL outcomes in clinical practice and research.
Key Words: Ambiguous genitalia, Congenital adrenal hyperplasia, Disorder of sex development, Quality of life, Endocrine, Gender Identity, Feminizing genitoplasty

Introduction

Congenital adrenal hyperplasia (CAH), an autosomal recessive disorder, is caused by genetic impairment of one of the 5 enzymes required for the biosynthesis of cortisol from cholesterol in the adrenal cortex. The most frequent enzyme deficiency in CAH is steroid 21-hydroxylase deficiency (21-OHD), accounting for more than 90% of cases.[1] The range of incidence for this condition is from 1:10,000 to 1:20,000 births and it is more prevalent in some ethnic groups (e.g., Alaskan Yupiks).[2–5] CAH is the commonest cause of ambiguous genitalia for female newborns and is one of several conditions under the umbrella term "Disorders of Sex Development" (DSD).

DSD refers to "congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical."[6] Management of DSDs require multidisciplinary collaboration and is challenging, to say the least. To date there has been a resurgence in research performed on these patients. One of the aspects of management brought up by those involved in the care of patients with DSDs are the need for more attention to be focused on the psychological aspects and quality of life of those affected.[6–8] There is a paucity of long-term outcome studies on DSD to inform on whether current management achieves optimal outcome.[9] This review on the research done on quality of life (QOL) of female patients with CAH aims to address the following issues: (1) to discuss possible factors affecting quality of life (QOL) of female patients with CAH, especially in the developing population; (2) to summarize the extant literature on the quality of life outcomes of female patients with CAH; and (3) to offer recommendations to improve QOL outcomes in clinical practice and research.

Congenital Adrenal Hyperplasia in Females due to 21-Hydroxylase Deficiency (21-OHD) and Factors Affecting their Quality of Life

Clinical Factors

A spectrum of phenotypes can be seen in 21-OHD; from the severe classical salt-wasting (SW) form, to the classical less severe simple-virilizing (SV), and to the non-classical forms (NC-CAH) which manifest during early adolescence.[10] All female patients with classical 21-OHD exhibit ambiguous external genitalia. Approximately two-thirds of

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patients with classical CAH due to 21-OHD have insufficient aldosterone biosynthesis, leading to salt-wasting crises postnatally.[3] This is characterized by life-threatening hyponatremia, dehydration, and shock. Hence, the salt-wasting type is the most severe clinical phenotype. Without early recognition and prompt medical treatment, patients with SW will die after birth whereas the SV forms will show progressive virilization with precocious puberty.

Patients with non-classical forms of 21-OHD present with partial deficiency of 21-hydroxylase activity, leading to the later onset of the disorder and milder clinical symptoms, without ambiguous external genitalia. In the peripubertal period, these affected girls may present with premature pubarche, tall stature, advanced bone age, menstrual irregularities, hirsutism, and acne, and later on also with infertility.[10] There are also very mild or asymptomatic forms.

These patients require life-long medications, for example, glucocorticoids with or without mineralocorticoids, and follow-up at specialist centers. Proper treatment with glucocorticoids prevents adrenal crisis and virilization and to enable normal growth and development.[11] Clinical management of classical CAH is, however, a challenging balancing act between suppressing hyperandrogenism and preventing hypercortisolism.

Associated Medical Problems

Certain features of this condition such as short final adult height, infertility, adrenomedullary insufficiency, obesity, and insulin resistance cannot be completely overcome by glucocorticoid treatment.[10,12] The current available therapy for 21-OHD does not achieve completely normal growth and puberty nor does it suppress effectively hyperandrogenism without causing the excessive effects of overtreatment, for example, Cushing syndrome.

Feminizing Genitoplasty

Female newborns with ambiguous genitalia are classified according to Prader scales which present different degrees of virilization.[12] Once the decision for the female sex of rearing has been made by the clinicians and parents, then these patients will undergo feminizing genitoplasty. This surgery entails operating on the enlarged phallus and the vagina, aimed to achieve near-normal appearance of functional genitalia enabling sexual relations and menstruation. The goals of surgery are to reduce the clitoromegaly, create the labia minora, and exteriorize the vagina.[13] The usual practice is that the clitoromegaly is performed prior to the vaginoplasty.[14]

The state of the art in reconstruction of ambiguous genitalia has evolved over the past few decades, with significant contributions from different surgeons. The components of reconstruction are clitoral reduction, the construction of the labia, and vaginoplasty.[14] The evolvement of surgical reconstruction of the prominent clitoris in the history of surgery has gone from simple amputation of the clitoris to techniques for concealment, plication, recession, and reduction with focus presently on not only producing a normal cosmetic appearance but also at preserving sensation and vascularity of the glans[14] and incorporating the preserved parts of the enlarged clitoris into the labia minora.[15–17] Similarly, many urologists have contributed to the state of the art in reconstructing the vagina. Vaginal reconstruction has evolved depending on the anatomy of the ambiguous genitalia with regards to the variability of the anatomy of the urogenital sinus (UG) with its confluence with the external sphincter of the bladder.[14]

Different Procedures in Feminizing Genitoplasty and Timing of Surgery

This surgical challenge may be approached either separately (i.e., a 2-stage procedure, where the clitoroplasty is performed in infancy followed by vaginoplasty delayed until near puberty) or as a 1-stage procedure (in which all 3 procedures, clitoroplasty, labioplasty and vaginoplasty, are performed in one setting in early childhood or infancy).

Recommendations about the proper timing of vaginoplasty vary: most reconstructive surgeons recommend a single-stage procedure, especially if the vagina is 'low,' when it can be exteriorized by a simple flap vaginoplasty as described by Fortunoff et al.[18] This technique is appropriate when the vagina reaches the UG sinus distal to the external urethral sphincter and can be brought to the flap with no tension. In patients where the urethra communicates with the urogenital sinus proximal to the external sphincter (high confluence or a 'high' vagina—less than 5%), other techniques, e.g., the 'pull-through' vaginoplasty by Hendren and Crawford [19] or the method described by Passerini-Glazel[20] are used to prevent incontinence.[13]

Different approaches to the high vagina have been described. Peña et al recommended the midsagittal posterior incision which involves splitting the entire rectum in the midline to provide improved exposure of the UG sinus.[21] Hendren later described mobilization of the rectum in the prone jackknife position, following this with its retraction posteriorly to expose the high vagina.[22] Rink et al describes a midline perineal prone approach to the high UG sinus that requires neither division nor mobilization of the rectum yet allows for excellent exposure of the high vagina.[23]

In 1997, Peña revolutionized vaginal reconstruction by advocating the "total urogenital sinus mobilization" (TUM); an "en bloc" urethra-vaginal pull-through procedure via a posterior sagittal approach, in treating patients with cloacal malformations.[24] Since then, there have been several modifications of this technique. Rink et al proposed "partial" urogenital mobilization (PUM) to reduce the risks of urinary incontinence that may result from the circumferential dissection of the UG sinus proximal to the pubourethral ligament that is done in TUM procedures.[25] He stated that in most cases this technique is adequate for repairs in girls with CAH and if necessary, PUM can be converted to TUM.[25]

The issue of timing for vaginoplasty, especially in those patients with a high confluence, has been controversial. Until recently, the majority of surgeons have recommended that those patients with a high UG sinus associated with