*Justine M Schober, MD**

# The Overvirilised Female

**UPMC Hamot, Erie, PA, USA*

## Introduction

Virilisation in an adolescent girl may be devastating socially, and psychologically. The most outward signs are hirsutism, acne, and secondary amenorrhea. Menstrual dysfunction, fertility issues, and hirsutism have been found to have adverse effects on emotional well-being, self-perception (including poor body image, self-consciousness, & low self-esteem), social functioning, and sexual behavior.[1] Hirsutism, generally associated with hyperandrogenemia, is most commonly caused by polycystic ovary syndrome (three out of every four cases), medication use, endocrinopathies, and neoplasms.[2] Though these characteristics may be worrisome to the typical teenager, they may not be the only symptom of over-virilisation.

More troubling still would be the onset of genital virilisation. In a female, this consists of the possibilities of clitoromegaly, posterior labial fusion, inguinal/labial mass, and various degrees of vaginal abnormality. It may result from CAH, as well as endogenous, and exogenous sources of androgens. Diagnosis of partially masculinized genitalia at birth was once considered a social emergency. However, the complexity of clinical diagnosis and studies of a multitude of long term outcomes have taught temperance. Notably influenced by cultural and ethnic issues, observations of some researchers suggest that most individuals who grow up with ambiguous genitalia—because surgery was not available—suffer from social stigmatization on a daily basis.[3]

A diagnosis of virilised genitalia represent a complex social, clinical, and sometimes surgical, challenge. Systematic clinical investigation considers chromosomal complements, hormone production, maternal conditions and exposures, patient exposures, and anatomical structures present when genital sexual differentiation has been affected.

Developmental biology discoveries have advanced our understanding of many anatomic details, though all malformations of the urinary and genital tracts are not yet explained by embryology. Some malformations can be related to hormonal changes introduced at particular stages of development. We continue to elucidate the genes, proteins and pathways related to sexual differentiation. The understanding of estrogen, glucocorticoid and androgen receptor status of vulvar and vaginal tissue is critical to understanding the structural development of masculinizing and feminizing characteristics of genital structures. However, it is also critical to understand medical and surgical therapy considerations impacting surface integrity of the vulvar/vaginal epithelium. Continuing elucidation of the embryology and immunohistochemistry of urogenital tissue may be a step toward the development of molecular tools to treat urogenital abnormalities.

## Chromosomes, Embryology, Hormones and Receptors

Sex differentiation can be divided into 3 phases, with chromosomal sex established at fertilization. Though it has long been held that ovarian formation is passive, an event that happens in the absence of testicular formation (but requiring two functional X chromosomes), it is possible that there is a counterpart to testis determining factor in females that determines ovarian differentiation. Deletions from Xp or Xq or from both have indicated that genes from both arms of the X chromosome are involved in ovarian differentiation and maturation.[4,5] On Xq in the paracentromeric region there is a location for androgen receptor protein and for X inactivation. In female mammals this is important for dosage inactivation of one X chromosome.[6] Random inactivation is fixed for each cell, and its progeny, so that each female is a mosaic of paternal, and maternal, active X chromosomes. Other genes such as WT-1, SF-1, SOX-9 and DSS play a role in sex determination. Wt-1 is active in development and maintenance of gonadal tissue effecting upstream of SRY. The presence of gonadal dysgenesis in XX Denys-Drash patients suggests that WT-1 is not sex specific.[7]

The second step is the differentiation of the gonads, followed by establishment of the phenotypic sex. Development of the reproductive tract begins in the embryo and is sex independent. In the human, the embryonic period spans weeks 2-8 of gestation .Until the fetus reaches 50mm CR-length (9 weeks) the genitalia in both sexes looks identical. Germ cells appear in the epiblast, migrate through the primitive streak and then to the base of the allantois. Along the wall of the hindgut, they migrate to the urogenital ridge. In the primitive gonad, primitive sex cords displaying a corticomedullary architecture are formed by the end of the 6th week.[8]

The third step is the development of the phenotypic sex, comprising internal and external genitalia. The XX gonad does not undergo any dramatic organizational change until follicle formation begins near birth.[9] Ovarian formation starts with the early fetal stage described by Jirasek as extending from the end of the embryonic period (the first week) until week 16 of gestation. During the first week, oogonia at the center of the gonad enter meiosis which rapidly extends peripherally to reach oogonia at the surface of the ovary. Two X chromosomes are not needed at this point.[10]

In the late fetal stage after 16 weeks, primary follicles begin to form in the ovary and are characterized by an oocyte. These are completely surrounded by a single layer of follicular cells and connective tissue. If the surround is incomplete the oocytes degenerate. Formation of primary follicles do require two X chromosomes. At the age of viability (24wks) some ovarian follicles consist of growing oocytes surrounded by several layers of granulosal cells. Stroma surrounding the growing follicles organize into theca interna and externa. At the end of gestation some follicles become vesicular, degenerate and disappear from the ovary within 6 months of birth. They represent again at the onset of puberty.[11] At both stages follicles can be detected by ultrasound if they are bigger than 2 mm. They constitute an organotypic pattern and are considered indicators for the presence of germ cells. Absence of germ cells is compatible with testicular development, but without germ cells ovary development does not take place and a streak gonad will result. The gubernaculum and the suspensory ligaments are relevant for the position of the gonad. Incomplete regression of the caudal suspensory ligament may contribute to the abdominal position of the gonads in some patients with XY DSD. These relations have been described in detail by Clarnette.[12]

***Reproductive Ducts: Mesonephric and Paramesonephric Ducts***

At the seventh week, development begins to diverge between the sexes. In the female fetus organogenesis involves regression of the mesonephric ducts and development as well as stabilization of the paramesonephric ducts. This proceeds in absence of testicular hormones. At the time of apparent male differentiation in an XY fetus, the comparable undifferentiated structures in the female are irreversibly committed to female organogenesis. This begins at the end of the embryonic period with fusion of the caudal ends of the two paramesonephric ducts with the urorectal septum. As soon as the paramesonephric ducts come into apposition with the urorectal septum, and begin to fuse, the uterus is forming, at about 63 days gestation. The cephalic ends develop fimbriae, the lower segment, the uterine tube, with transverse lie established by descent of the ovary.[13] The genital canal is established at about 80 days with absorption of the median septum. It lenghthens and its caudal end continues to grow and contacts the posterior wall of the urogenital sinus. With additional cellular proliferation, the vagina is formed. The cervix (caudal two-thirds of the fetal uterus) may be from either paramesonephric or urogenital sinus origin.[14]

***Development of the External Genitalia***

The initial signs of masculinization are an increased distance between the anus and the genital structures. Circulating androgens and conversion to dihydrotestosteron induce the genital tubercle to grow. Tubularisation of the urethral plate leads to formation of the urethra. Between 63 and 77 days feminization or differentiation from the masculinized form begins. The clitoris does not lengthen but instead bends forward or caudally. Before 20 weeks there is a slow phase of growth of the genital swellings that covers the superior and lateral aspects of the clitoris . Anogenital distance does not change but the phallic portion of the urogenital sinus remains open and the genital folds do not fuse. At some time between 14 and 20 weeks the vagina opens into the pelvic portion of the urogenital sinus and it becomes the vaginal vestibule[15,16] Next, ovarian follicular growth begins (20-22 weeks), there is rapid ventral outgrowth of the perineum, the urethral and vaginal openings separate, and urethral and vaginal openings are brought to the surface. During this process the clitoris becomes incorporated in the fused anterior ends of the genital folds (labia minora). The labia minora continue their growth posteriorly. Genital swellings lateral to labia minora become the labia majora continuous anteriorly as the mons pubis. Growth of the labia minora is greater than that of the labia majora during this time and they are seen protruding out of the labia majora at 23-25 weeks gestation. After 26 weeks the labia majora have grown sufficiently to cover the labia minora.

Studies of time sequence of female phenotypic differentiation and ovarian hormones suggest a role for ovarian hormones in female phenotypic development. At midtrimester there is no difference in distribution of androgen receptors between male and female fetuses in the external genitalia. At this time estrogen receptors are present only in the genitalia of the female fetus. It is not known when estrogen receptors appear or what induces their appearance. Their lack may be what protects male fetuses from the effects of maternal estrogen.

The development of a bladder and urethra separate from the vagina requires the growth of a membrane from cranial to caudad in the urogenital sinus. Anomalies of female embryogenesis during this process lead to a variety of clinically recognized disorders. Some may be seen antenatally by ultrasound examinations, others at physical examination of the vaginal introitus in the newborn. Those that are visually and functionally less obvious, may not be recognized until the development of clinical problems such as urinary incontinence, pelvic pain, lack of onset of menses, and sexual difficulties.

In the female fetus organogenesis involves regression of the mesonephric ducts with development, as well as stabilization, of the paramesonephric ducts. This proceeds because of the absence of testicular hormones. At the time of apparent female differentiation in an XX fetus, the comparable undifferentiated structures in the female are irreversibly committed to female organogenesis.[17,18]

Growth and development of the genitalia are influenced by hormones, as estrogen is responsible for vascularity and thickness of vaginal tissue.[19] Labia minora are the female homologue of male genital structures that undergo ventral folding and fusion to form the penile urethra and corpus spongiosum. Failure of the labia to fuse in the normal female fetus may be due in part to the lack of fetal androgen production and low 5-alpha reductase activity, (in part due to maternal estrogen stimulation of ER-positive urethral folds) causing the labia minora to diverge laterally. There is extensive circumstantial evidence that 17-beta estradiol and also progesterone influence the postnatal physiology of extra genital and especially genital (vulval) skin in the human female.[20] ER positivity in the fetus has been demonstrated in the stroma of the labia minora (highest concentration of ER) and in the periphery of the glans and inner prepuce.[21]

## Fetal Sources, Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a disorder of sexual development with a prevalence of one in 15,000 births world-wide. It is associated with a deficiency in 21-hydroxylase and consequent virilization as the external genitalia are competent to respond to DHT. The milder enzyme deficiency was termed nonclassical 21-hydroxylase deficiency (NC21OHD) in 1979 and later found to be the most common autosomal recessive disorder in humans. Disease frequency of NC21OHD varies between ethnic groups with the highest ethnic-specific disease frequency in Ashkenazi Jews (one in 27).[22] NC21OHD is diagnosed by serum elevations of 17-OHP and confirmed with molecular genetic analysis. Females with 'classical' 21-OHD, are exposed to excess androgens prenatally, and are born with virilised external genitalia. Potentially lethal adrenal insufficiency is characteristic of two-thirds to three-quarters of patients with the classical salt wasting (SW) form of 21-OHD. Non-SW 21-OHD may be diagnosed on genital ambiguity in affected females, and/or later on the occurrence of androgen excess in both sexes. A deficiency of 11-beta-hydroxylase is the second most common cause of CAH, virilisation may be mild or as severe as seen in classical 21-OHD. Another CAH variant, p450 oxidoreductase deficiency may also result in ambiguous genitalia. This variant shows mixed features of the above mentioned causes of CAH and is associated with Antlye Bixler craniosynostosis. All forms of CAH have intact mullerian structures and ovaries. There are other less common genetic causes of 46 XX virilisation which include SRY translocation, SOX-9 duplication, and mutations in the glucocorticoid receptor nuclear transcription factor. SRY translocation results in testes or ovotestis and lack of Mullerian structures. SOX-9 duplication may cause testicular differentiation in the XX female with the absence of SRY.[23] Mullerian structures are absent in SOX-9 duplication. In SRY translocation and SOX-9 duplication external genitalia is masculinized or ambiguous.

Virilisation of prepubertal girls that is not due to congenital virilising andrenal hyperplasia is usually caused by androgens arising from an abnormality of the adrenal glands or ovaries. Adrenocortical oncocytoma is extremely rare, accounting for less that 0.2% of all pediatric neoplasms. It can result in virilisation and pseudopuberty, with high levels of DHEA. The tumor is treated with resection and although it has little malignant potential the long term history is not yet known.[24] Stein-Leventhal syndrome should also be considered in the differential diagnosis of virilization in prepubertal girls.[25] Genital virilization such as clitoromegaly can be a result of factors other than chromosomal abnormalities, androgen exposure, or maternal luteomas. Genitourinary neurofibromatosis with clitoral involvement appears more commonly than reported, and should be involved in the differential diagnosis of ambiguous genitalia.[26] Most fetus' are protected from maternal androgens by aromatase from the placenta. A syndrome of aromatase deficiency from a molecular defect in CYP19 (p450arom) in the 46, XX female results in the inability to transform androgens to estrogens.[27] Limited data show that levels of androgen in cord blood show the most direct relationship to the virlised female fetus.

**TABLE 1. Maternal or Exogenous Sources of Androgens**

| |
|---|
| PCOD |
| Other sources of masculinization with resultant ambiguous genitalia |
| Embryonic exposure to fungicide vinclozolin |
| MPA |
| Lipoid cell tumor of the ovary |
| Parent using cutaneous androgen preparations |
| Pregnancy luteomas |
| Off label "appetite stimulant" cyproheptadine and methandienone (a derivative of testosterone) |
| Methandrostenolone containing cream for excema |
| Adrenal myelolipomas |
| Choriocarcinoma |
| Adrenocortical carcinoma |
| Testosterone-secreting adrenal adenoma |
| Placental site trophoblastic tumor (adult) |
| Adrenal ganglioneuroma |
| Granulosa tumor of the ovary |
| Massive ovarian edema |
| Hyperthecosis ovarii |

## Maternal or Exogenous Sources of Androgens

Other sources of virilisation with resultant ambiguous genitalia may come from androgenic stimulation from non-fetal sources. Fetal virilisation occurs during a critical period between weeks 8 and 13 weeks of gestation and results in labioscrotal fusion and urogenital sinus formation. Excess androgen exposure before 12 weeks can cause labial fusions and development of phallic urethra or virilized urogenital sinus. Androgen exposure after week 12 will result in clitoralomegaly and scrotalization of labial folds. Female embryos have the same androgen receptor system in the urogenital tract as male embryos, therefore, administration of androgens at the appropriate time during embryogenesis may cause profound virilisation. However, internal genitalia are not masculinized and Wolffian duct remnants are normal.

Although congenital adrenal hyperplasia is the most common cause of masculinization in a female fetus, masculinization as a consequence of a maternal hormone-producing tumor is becoming a more frequently recognized clinical entity. Masculinizing ovarian tumors may include; luteoma of pregnancy, granulosa tumor, arrhenoblastoma, hilar cell tumor, lipoid cell tumor, masculinizing ovarian stromal cell tumor.[28] Luteoma of pregnancy is the most common. These tumors are always benign, can be multiple, and are frequently bilateral, occuring more often in multiparas.[29] For women who have histories of pregnancy with luteoma that have resulted in a virilised female fetus, a possible solution may be fertilization with pre-selected Y-spermatozoa. Other virilising tumors which are maternal sources of androgens that induce virilisation include; Krukenberg tumor, adrenocortical carcinomas, adrenal myelolipomas, ganglioneuromas, choriocarcinoma, testosterone-secreting adrenal adenoma, and placental site trophoblastic tumor. Bilaterality and multinodularity are more common in luteomas than in these other tumours. Polycystic ovary Syndrome (PCOS), and massive ovarian edema are also described as a sporadic cause of virilisation during pregnancy. Unfortunately, independent of cause, there is no treatment available to correct virilization once it has occured during pregnancy.

Maternal ingestion of androgens, progestagens (those with the 19-nor structure are most androgenic), and drugs such as danazole, stilboestrol, 1-9-nortestosterone (for threatened abortion) may cause labial posterior fusion, clitoromegaly and more pronounced virilisation.[30] Ingestion of the off-label "appetite stimulant" cyproheptadine and methandienone (a derivative of testosterone) has been cited as a source of fetal virilization.[31] Maternal application of topical preparations, and exposures to topicals noted to induce virilisation of the female fetus

include; cutaneous androgen preparations, methandrostenolone containing cream for excema, and exposure to the fungicide vinclozolin.[32] Only 65% of virilised mothers deliver virilised female infants. Protective mechanisms such as active placental aromatization of androgens into estrogens, maternal metabolism of androgens, increases in androgen binding proteins (SBP and SHBG) under the influence of placental estrogens, and the protective buffering effect of the high concentrations of estrogens found in the fetal blood, might be responsible for the protection of the fetus against virilisation.

## Treatment of the Overly Virilised Female

Virilization of the female genitalia may vary widely in severity as measured by the Prader Scale. This scale ranges from 0 (the unvirilised female), to 5 (the completely virilised female). Issues of an appearance of gender typicality have been debated for parent and patient concerns, with risk to genital sensory function weighed against cosmesis. Timing, staging and separating clitoroplasty, and vaginoplasty, (allow patient input, decrease unwanted surgery and revisions) continue to be at issue. Simple clitoromegaly or very distal entrance of the vagina into the urogenital sinus may require no treatment. In more virilised forms (as the vagina enters the urogenital sinus more proximally and nearer the bladder neck), typical intercourse may be impossible. Reconstructive surgery may be necessary to establish sexual capability(if desired by the patient). It has become evident that a completely successful feminizing genitoplasty may require multiple revision surgeries (50-79% of patients required a second procedure). Third and fourth procedures are not uncommon for adequate vaginal construct which allows intercourse. About 77% of those who had this surgery ultimately had an adequate vaginal introitus on long term follow up. Scarring at the introitus or of the entire vaginal segment has been a problem. This complication is most prevalent when local skin flaps and squamous epithelial grafts are used to create portions of the vagina, and in some cases the entire vagina. Surgery to construct a neovagina carries a risk of neoplasm.[33] In the overvirilised 46XX female, gender assignment is usually female. In managing the most severely virilised patients (ambiguous genitalia), guidelines proposed by Meyer-Bahlburg (1999) should be recalled, considering five important patient centered factors; reproductive potential, good sexual function, minimal medical procedures, an overall gender appropriate appearance, stable gender identity, and psychosocial well-being.[34] Cultural and social factors must also be addressed. It has been shown that virilised patients may value being able to discuss their condition with others who have had the same condition. Such early intervention may be especially important for children. Forming relationships with similarly affected children may enhance a feeling of openness and normalcy early on. Support groups also help in finding the best quality of care. Focus on recognition of the diversity of normal genital appearance and function, as well as, efforts to eliminate or deal with social stigma, and cultural factors, by an experienced healthcare team can best address the needs of the individual.

## References:


1. Bode D, Seehusen DA, Baird D. *Hirsutism in women.Am Fam Physician,* 85(4): 373-380. 15 February, 2012, Review.
2. Jones GL, Hall JM, Lashen HL, Balen AH, Ledger WL. Health-related quality of life among adolescents with polycystic ovary syndrome. *J Obstet Gynecol Neonatal Nurs,* 40(5): 577-588. doi: 10.1111/j.1552-6909.2011.01279.x. September-October, 2011.
3. Callens N, van der Zwan YG, Drop SL, Cools M, Beerendonk CM, Wolffenbuttel KP, Dessens AB. Do surgical interventions influence psychosexual and cosmetic outcomes in women with disorders of sex development? *ISRN Endocrinol*, 2012: 276742 Epub, 5 March, 2012.
4. MacLaughlin DT & Donahoe PK. Sex determination and differentiation. *The New England Journal ofMedicine,* 350(4): 367–378, 2004.
5. Federman DD. The biology of human sex differences. *The New England Journal of Medicine,* 354(14): 1507–1514, 2006.

6. Ferguson-Smith MA. Karyotype–phenotype correlations in gonadal dysgenesis and their bearing on thepathogenesis of malformations. *Journal of Medical Genetics,* 2: 142–155, 1965.
7. Wilhelm D & Koopman P. The makings of maleness: towards an integrated view of male sexual development. *Nature Reviews Genetics,* 7(8): 620–631, 2006.
8. Donahoe P. Perspective: reproductive tract development – new discoveries and future developments.*Endocrinology,* 142(6): 2167–2172, 2001.
9. Ammini AC, Pandey J, Vijyaraghavan M *et al.* Human female phenotypic development: role of fetal ovaries. *The Journal of Clinical Endocrinology and Metabolism,* 79(2): 604–608, August, 1994.
10. Jirasek JE. Development of the genital system in embryos and fetuses. In Cohen MM (ed.). Development of the genital system and male pseudohamaphroditism. *Baltimore: Johns Hopkins Press*, pp., 3–23, 1971.
11. Ammini AC, Pandey J, Vijyaraghavan M *et al.* Human female phenotypic development: role of fetal ovaries. *The Journal of Clinical Endocrinology and Metabolism,* 79(2): 604–608, August, 1994.
12. Clarnette TD, Sugita Y, Hudson JM *et al.* Genital anomalies in human and animal models reveal themechanisms and hormones governing testicular descent. British Journal of Urology, 79(1): 99–112, 1997.
13. Witschi E. Development and differentiation of the uterus. In Mack HC (ed.). Prenatal Life. *Detroit:Wayne State University Press*, pp.: 11–35, 1970.
14. O'Rahilly R. The development of the vagina in the human. In Blandau RJ & Bergsma D (eds.). Morphogenesis and Malformation of the Genital System. *New York: Liss*, pp.: 123–136, 1977.
15. Perriton CL, Powles N, Chiang C *et al.* Sonic hedgehog signaling from the urethral epithelium control external genital development. *Developmental Biology,* 247: 26–46, 2002.
16. Hunter RH. Observations on the development of the human female genital tract. *Contributions to Embryology,* 22: 91–108, 1930.
17. Brennan J & Capel B. One tissue, two fates: molecular genetic events that underlie testis versus ovarydevelopment. *Nature Reviews Genetics,* 5(7): 509–521, 2004.
18. Val P & Swain A. Mechanisms of Disease: normal and abnormal gonadal development and sex determination in mammals. *Nature Clinical Practice Urology,* 2(12): 616–627, 2005.
19. Farage M, Maibach H. Lifetime changes in the vulva and vagina. *Arch Gynecol Obstet,* 273(4): 195-202. Epub 2005 Oct 6., January, 2006 Review
20. Farage MA, Maibach HI *Morphology and physiological changes of genital skin and mucos Curr Probl Dermatol,* 40: 9-19. Epub 2011 Feb 10, 2011.
21. Kalloo NB, Gearhart JP, Barrack ER Sexually dimorphic expression of estrogen receptors, but not of androgen receptors in human fetal external genitalia. *J Clin Endocrinol Metab,* 77(3): 692-698, September, 1993.
22. Witchel SF, Azziz R Congenital adrenal hyperplasia. *J Pediatr Adolesc Gynecol,* 24(3): 116-126, June, 2011.
23. Seeherunvong T, Ukarapong S, McElreavey K, Berkovitz GD, Perera EM. Duplication of SOX9 is not a common cause of 46,XX testicular or 46,XX ovotesticular DSD. *J Pediatr Endocrinol Metab,* 25(1-2): 121-123, 2012.
24. Lim YJ, Lee SM, Shin JH, Koh HC, Lee YH.Virilizing adrenocortical oncocytoma in a child: a case report. *J Korean Med Sci.,* 25(7): 1077-1079. Epub 2010 Jun 17, June, 2010
25. Hoyt KL, Schmidt MC. Polycystic ovary (Stein-Leventhal) syndrome: etiology, complications, and treatment. *Clin Lab Sci.,* 17(3): 155-163, Summer, 2004, Review.
26. Kantarci M, Alper F, Aliagaoglu C, Yildirim U, Onbas O, Sivri F. Neurofibromatosis of the labium majus and clitoris: an unusual image reminiscent of ambiguous genitalia.*Acta Obstet Gynecol Scand,* 84(1): 96-98, January, 2005.
27. Kalfa N, Méduri G, Philibert P, Patte C, Boizet-Bonhoure B, Thibaut E, Pienkowski C, Jaubert F, Misrahi M, Sultan C.Unusual virilization in girls with juvenile granulosa cell tumors of the ovary is related to intratumoral aromatase deficiency.*Horm Res Paediatr,* 74(2): 83-91. Epub 2010 April 15, 2010.
28. Hicks ML, Danzey TJ. Hormonally Active Organ Tumors in Children and Adolescents. *Adolesc Med.* 5(1): 131-142, February, 1994.

29. Masarie K, Katz V, Balderston K. Pregnancy luteomas: clinical presentations and management strategies. *Obstet Gynecol Surv,* 65(9): 575-582. September, 2010, Review.
30. Rosa FW. Virilization of the female fetus with maternal danazol exposure. *Am J Obstet Gynecol,* 1, 149(1): 99-100, May, 1984.
31. Poomthavorn P, Mahachoklertwattana P, Khlairit P Childhood virilization and adrenal suppression after ingestion of methandienone and cyproheptadine. *J Pediatr Endocrinol Metab.,* 22(5): 459-462, May, 2009.
32. Sorgo W, Zachmann M. Virilization caused by methandrostenolone-containing cream in 2 prepubertal girls]. *Helv Paediatr Acta.,* 37(4): 401-406. Septermber, 1982, German.
33. Schober JM. Cancer of the neovagina. *J Pediatr Urol.* 3(3): 167-170, Epub 2006 Nov 7, June, 2007.
34. Meyer-Bahlburg HF. *Health-related quality of life in intersexuality Acta Paediatr Suppl.,* 88(428): 114-115, February, 1999.