Congenital genital anomalies. Aspects of diagnostics and treatment

Indrė Zaparackaitė, Vidmantas Barauskas
Clinic of Pediatric Surgery, Kaunas University of Medicine, Lithuania

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Summary. *Congenital genital anomalies are a very complex pathology. In order to clarify its causes it is important to revert to the genetic conditions and regularities of embriological development. The genital disturbances are mostly determined by chromosomal or endocrinic disorders or by impaired biochemical processes. Clinical problems arise when the genetical sex is in discrepancy with ambiguous genitalia. True hermaphroditism, congenital adrenal hyperplasia, testicular feminization and gonadal dysgenesis are the most common syndromes. Diagnostic criteria applied are similar for all (establishment of karyotype, investigation of hormones and their derivates, genital ultrasound and endoscopy, if needed – radiological examination), but medical and surgical treatment is applied to each patient individually.*

The spectrum of congenital genital anomalies is really broad. Therefore a reliable classification helps to be guided among subtle differences. Compared to other well-described clinical entities such as inguinal hernia or appendicitis, the diagnosis of genital anomalies is usually much more complex. The term "intersex" is widely used for description of different conditions related to sexual maldevelopment. The most conspicuous are those with such ambiguity of the external genitalia that the gender is not easily determined. The most common changes of external genitalia and their possible causes are listed in Table 1 and 2.

There are four main types of genital anomalies:

1. True hermaphroditism (the individual has both ovarian and testicular tissue).
2. Male pseudohermaphroditism (male genotype, female phenotype).
3. Female pseudohermaphroditism (female genotype, male phenotype).
4. Gonadal dysgenesis (occurs due to aberrant chromosomes, may be present with miscellaneous clinical symptoms).

An understanding of the normal development helps in clarifying the possible causes of genital maldevelopment. In this paper we are going to pay an extra attention to the questions of gender assignment and congenital female genital anomalies because the problems of undervirilization including hypospadias and cryptorchidism are widely discussed elsewhere.

At the beginning of human development the genital structures are identical. The genital differentiation leading to male or female gender formation starts at the 7-8th and ends at about the 12-15th week. The first important factor in sex determination is the sex chromosome. The spontaneous fetal genital development is female, and every single fetus will develop female characteristics. At the embryological start the Müllerian and Wolffian structures co-exist. However, under normal circumstances the Y chromosome contains a sex reversal gene (SRY) and is also responsible for the testicular production of testosterone (secreted by Leydig cells) and the Müller inhibiting substance (MIS, secreted by Sertolli cells), now mostly called anti-Müllerian Hormone (AMH) (14). These substances will cause development of the male genital structures from the primitive Wolffian ducts and atrophy of the Müllerian structures (the Fallopian tubes, the uterus and the vagina), starting from the 7th week. Clinical problems arise due to discrepancy between chromosomal sex, gonadal differentiation and apparent phenotypic alterations. If for any reasons the testicular tissue does not differentiate till the 12th week or it does not function, the result will be a female phenotype (3, 16, 30). Any mosaic or deviation from normal may lead to congenital anomalies of internal genitalia and influence the external alterations. Sometimes even with a normal chromosomal set, the phenotype may be different from

Correspondence to I. Zaparackaitė, Clinic of Paediatric Surgery, Kaunas University of Medicine, Eivenių 2, 3007 Kaunas, Lithuania

Table 1. **Most common causes of ambiguous genitalia in 46XX infants**

Problem	Cause
Fetal androgen overproduction	Congenital adrenal hyperplasia Testis or ovotestis present
Androgens crossing placenta	Maternal virilizing disease or ingestion of virilizing drugs
Non androgenic	Isolated clitoromegaly due to neurofibromatosis

Table 2. **Most common causes of ambiguous genitalia in 46XY infants**

Problem	Cause
Insufficient androgen production	Gonadal dysgenesis (due to SRY mutation) Block in testosterone biosynthesis Primary Leidig cell dysplasia
Insufficient response to androgen	Abnormal androgen receptors (partial androgen insensitivity) Dificient conversion of testosterone to DTH (due to deficiency of 5α-reductase)

the genetic sex. From the biological point of view an individual could be considered to be a female if the masculine features have not developed. This paradoxical statement could also be explained embryologically (Figure 1) (30).

The purpose of this article is to describe the most common varieties of complex genital anomalies, discussing their diagnosis and the aspects of contemporary management.

Here we present a few most common types of genital anomalies, illustrating their different origin.

True hermaphroditism

True hermaphroditism is quite common in some animal species. It may also be found in humans but is then considered to be pathological. True hermaphrodites possess both ovarian and testicular tissue. Various types of pathology are possible: 2 gonads of mixed structure (ovotestes), 1 ovary and 1 testicle, one mixed and another normal gonad – either an ovary or a testicle (27). The ovotestes have a special histological structure – the ovarian tissue is situated centrally while the testicular tissue is in the poles. Those particular gonads seldom get malignant. The number and composition of the chromosomes might be absolutely normal but could also be mosaic. The most common finding is 46XX (90%) (8). The uterus is often found together with male internal genitalia and at puberty the patient may start menstruating and show breast tissue development. The abnormal internal genitalia may also influence the ambiguous looks with the features of both sexes. The condition provokes an essential question – what treatment do those patients require? Often it depends on the time when the diagnosis is established. If possible, all necessary investigations should be performed in early infancy and all decisions concerning sex of rearing should be made as soon as possible because otherwise multiple psychological and physiological problems may arise. In all cases the treatment is quite long and often life-lasting, especially if the hormonal replacement is applied. Surgical treatment is often required.

It is not easy to establish the diagnosis of true hermaphroditism, especially if the external alterations are not obvious. Sometimes the unusual structures are found incidentally during surgery, for example herniotomy or orchidopexy. In some cases the uncharacteristic structures are found by ultrasound or laparoscopy or the patient may present with amenorrhea. When the specialists and the parents

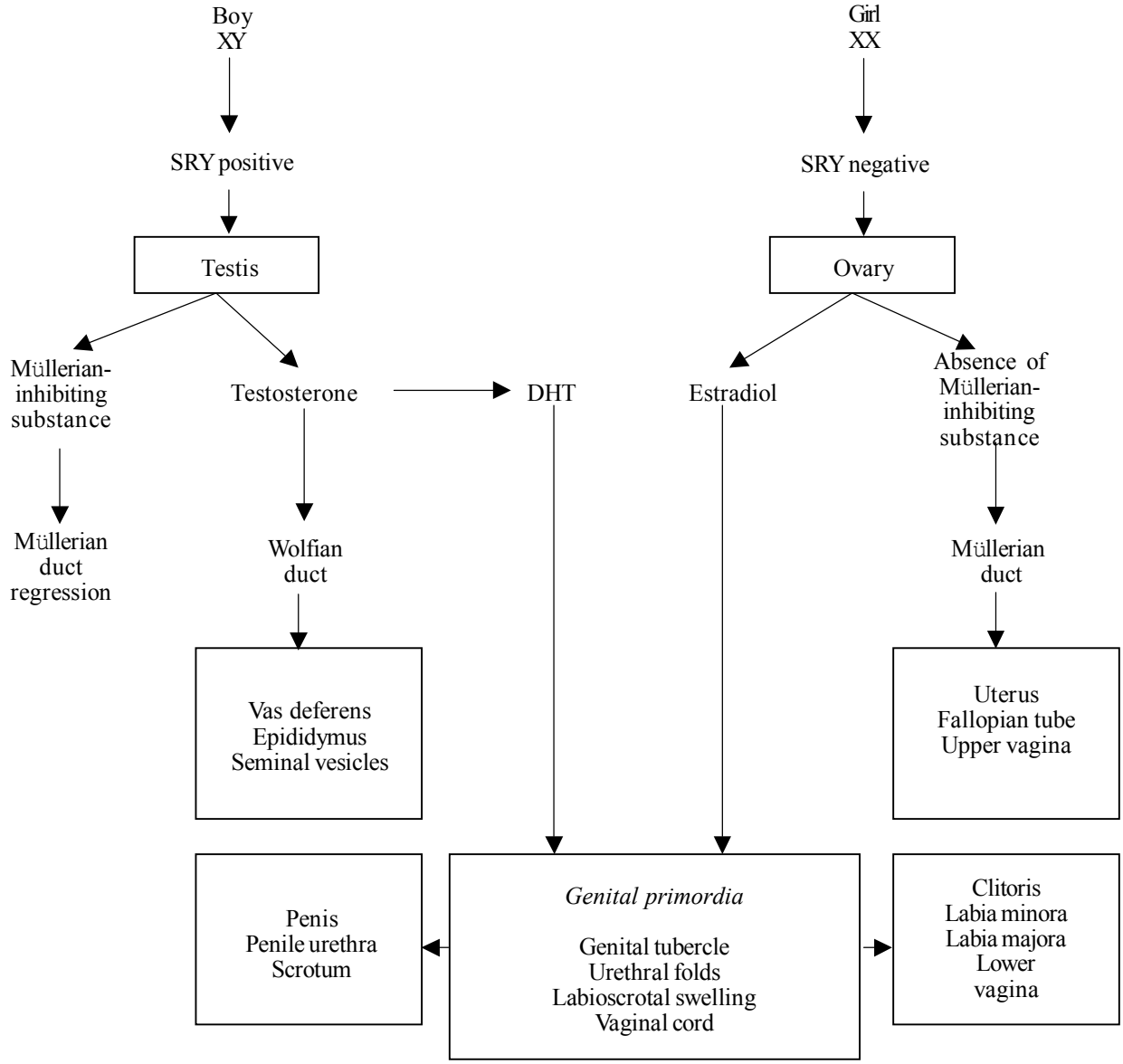

Fig1. **Scheme revealing the embryological principles of sexual development**

agree upon the sex of rearing, the genitalia of the opposite sex should be removed.

Apart from gonadal surgery reconstructive procedures on the external genitalia, male or female, may be indicated, according to the individual pathology.

Female pseudohermaphroditism

Adrenogenital syndrome (AGS), or congenital adrenal hyperplasia (CAH), is the most frequent cause of female pseudohermaphroditism with an incidence of 1:15000 (12).

This condition occurs due to a disturbance of hormonal production.

The main type of AGS occurs due to impaired cortisol synthesis from cholesterol because of enzyme 21-hydroxylase deficiency. The syndrome affects both sexes (12), but males never develop genital anomalies.

AGS can be present in several types; the most common is the salt wasting. Although soon after birth it is possible to establish an elevated level of specific enzyme 17-OHP (>100 nmol/l while normal is <5 nmol/l), the clinical symptoms usually appear later, when a newborn is 1-2 weeks old. Although the hormone and enzyme unbalance is present already before birth, the clinical symptoms usually first appear during the second and third week after birth. The baby will feed poorly and may present with copious vomiting. There is significant fluid loss, the plasma values of sodium are decreasing rapidly and the patient is usually admitted to the hospital

in shock. Those heavy consequences may be avoided if the diagnosis is established prenatally. Then the mother is given dexamethasone orally 10-20 mg/kg/day to suppress maternal estriol secretion and stimulation of the fetal adrenal glands. In case of AGS the internal genitalia in girls are of the female type, but the process of genital maturation is usually slowed down. The appearance of the external genitalia depends upon the virilizing action of androgens.

The Prader classification, Figure 2 (12), includes 5 different degrees of virilization.

I° – Hypertrophic clitoris with otherwise normal female genitalia,

II° – Hypertrophic clitoris, urogenital sinus, vaginal and urethral openings covered,

III° – Hypertrophic clitoris, narrow and deep urogenital sinus, high urethrovaginal confluence,

IV° – Phallo with small urogenital opening,

V° – Male genitalia.

In order to establish the diagnosis, certain parameters should be measured or examined. The most important are: assessment of hormonal status, genital examination, ultrasound, and very important – endoscopy, which could be combined with a contrast study, also radiological establishment of the "bone age", which may differ from the biological age: excessive androgen overproduction influences an intensive bone mineralization and enforces bone maturation. Endoscopy is the best way to find the level of the urethral and vaginal confluence. This anatomical feature is important for the surgical tactics. Each patient needs an individual approach. A low sinus requires a simple cutback procedure while a high sinus requires a total urogenital sinus mobilization (TUM). This procedure has the advantage of preserving the anatomical balance between the urethra and the vagina (19). Since most dissection is performed bluntly the risk of urinary incontinence is minimal. In case of suprasphincteric confluence high vaginal pull-through is required. Only very rarely vaginal substitution, for instance with sigmoid colon, is needed.

Male pseudohermaphroditism

Male pseudohermaphroditism occurs when male genitalia are not developed in genetically male individuals (46XY). The result is female phenotype.

The causes of this condition are:

1. Insufficient production of testosterone, when the process of biosynthesis is disturbed or testicular tissue underdeveloped.

Androgen production is insufficient due to a genetic defect of the enzymes involved in converting cholesterol into testosterone. The best-known enzymes involved are the following ones: 3β-hydroksisteroid hydrogenase, 17α-hydroksilase/17-20lyase and 17β-hydroksisteroid hydrogenase (20). A chorionic gonadotropin (hCG) test will show if functioning testicular tissue is present. In these patients the hCG test is negative while MIS/AMH levels are normal.

2. Disturbed synthesis of dihydrotestosterone (DHT) from testosterone in the target tissue under testosterone impact.

This is usually due to a deficiency of the enzyme 5α-reductase. In this situation a genetical 46XY individual has more female features, the male genitalia are underdeveloped: the scrotum resembles the labia majora and the small penis looks more like a clitoris. A small utricle in the posterior urethral wall may also be found. This may be a source of recurrent infections, in which case it needs to be removed. At puberty the testosterone level in those patients may be found to be normal, unless the gonads were removed before (33).

3. Insensitivity of androgen receptors – although there is a sufficient amount of testosterone, it cannot really affect the target receptors.

The androgen insensitivity syndrome may be complete (CAIS) or partial (PAIS). At present it is known more than 100 mutations at the androgen receptor gene (10). The incomplete forms are more common but also more difficult to diagnose. The appearance of those individuals might be ranging from almost normal female to nearly male (10, 31). In these cases the uterus is rarely found but a vaginal rudiment may be present. At puberty boys may present with pronounced breast tissue while the penis is developing very slowly. In some situations the penis is so small that boys cannot void while standing and this causes great psychological discomfort. Those patients usually require staged surgery.

Complete androgen insensitivity syndrome is also called Morris syndrome. In different parts of the world its incidence varies from 1:2000 to 1:60.000 (3, 25).

Diagnosis is usually established either during inguinal herniotomy or because a girl presents at puberty with absence of menstruations. In order to establish the precise diagnosis a skin specimen is obtained from the pubic area, labium majus or prepuce. The level of testosterone in blood serum can be elevated while the level of Müllerian inhibiting substance is elevated or normal (8).

Since true diagnosis as a rule is established pretty late usually there is no point of changing the sex of rearing. On the other hand it is recommended to re-

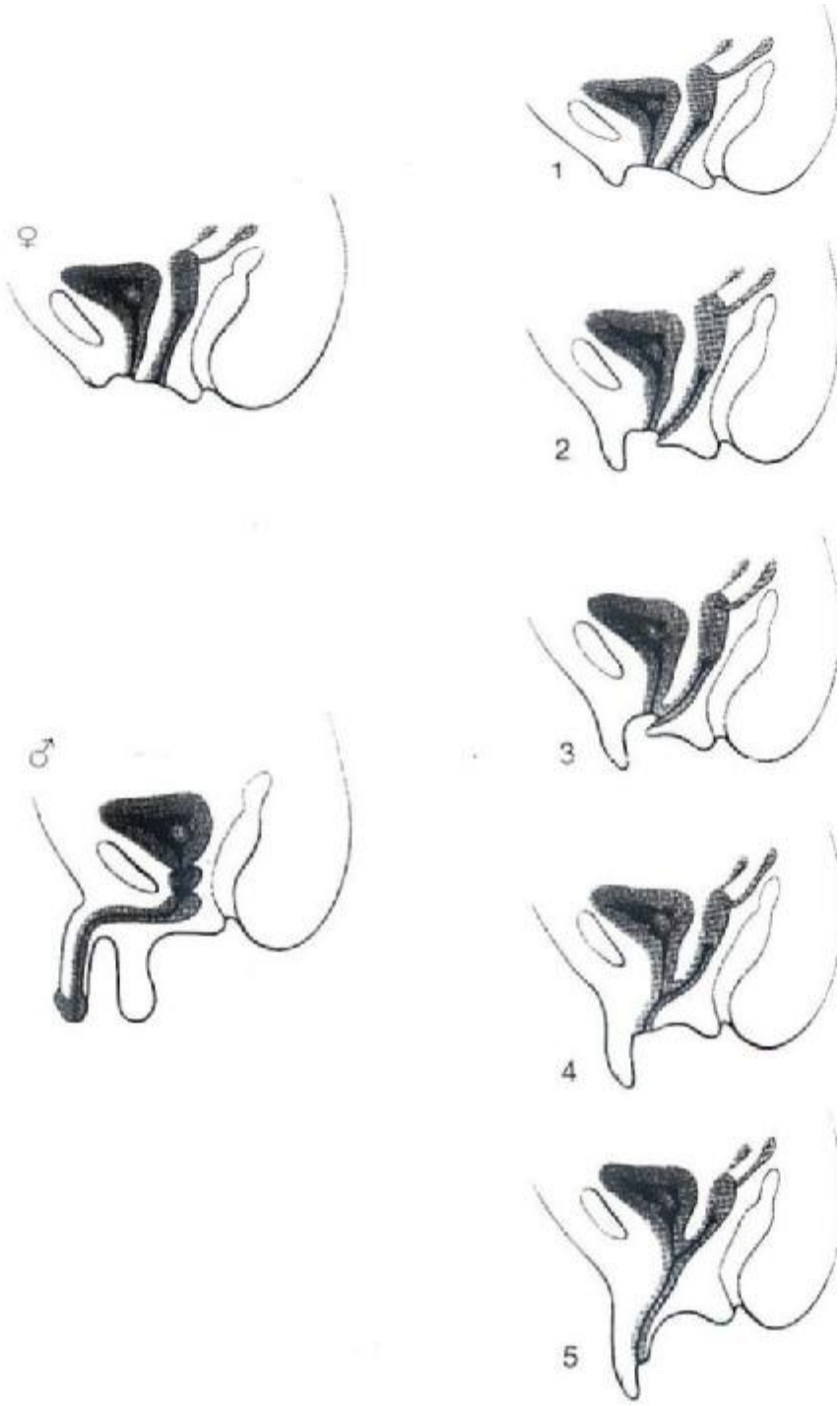

Fig. 2. **Scheme revealing external genital anomalies after Prader**
Left column: ♀ – normal female genitalia, ♂ – normal male genitalia; right column: intermediate stage ranging (top to bottom)from the near-normal female type (1) to the near-normal male type (5).

move male genitalia, to create a vagina and prescribe estrogen replacement therapy. In many cases the vagina may be created simply by stretching the existing vaginal pit, and this is to be preferred when possible. Otherwise substitution by other tissue is indicated. In pediatric urology sigmoid vaginoplasty is the preferred method.

Gonadal dysgenesis

Gonadal tissue in patients affected by gonadal dysgenesis mostly contains the connective tissue and therefore is different from that of true hermaphroditism. The Müllerian and Wolffian structures co-exist and the internal genitalia are underdeveloped. This could be explained by the fact that the abnormal go-

nad is secreting a low amount of MIS/AMH, so that any existing rudiment of a uterus cannot undergo full development. The gonads themselves are usually smaller compared to normal, often looking just like streaks. In case of pure gonadal dysgenesis both gonads are streaks. If both gonads are underdeveloped, then production of both testosterone and MIS/AMH is insufficient, and the level of gonadotropins in blood serum will be high (compensatory reaction). The most common finding is an underdeveloped testicle and a streak ovary, but other varieties are also possible: bilateral streak gonads, a tumor on one side and an underdeveloped gonad at the other side, or one normal gonad with a tumor on contralateral side (32).

In mixed gonadal dysgenesis the chromosomal structure is 46XY in 31%. In the rest the structure is mosaic, with 45X0/46XY as the most frequent pattern (35% of all cases).

It is important to notice that gonadal karyotype may differ from the one in blood and it may have a significant impact on the choice of treatment tactics, having in mind that the Y chromosome carries a risk of malignancy (2, 14, 21, 26, 30, 32). This is so when the gonads are abnormal, even with just a small particle of Y chromosome. The malignant development may first be carcinoma in situ, later gonadoblastoma, which if untreated may develop into malignant germinoma or seminoma (29, 30). The rate of malignancy reported in the literature is as high as 16-30% (2). Sometimes malignancy is present already in the neonatal period (8), but the greatest risk occurs at puberty. Therefore it is recommended to remove the abnormal gonadal tissue before that time. However, gonadectomy should not be performed just on clinical grounds, only after histological documentation of the pathology.

The attitude towards gonadal removal might vary according to the patient's sex and gonadal structure. Streak or slightly more developed gonads in girls should be removed and replacement hormonal treatment prescribed. In boys the streak gonads are removed but the testicles are left in the scrotum and a follow up regime arranged. It is proven that in case of MGD fixation of the undescended testicle does not protect against the occurrence of a malignant tumor (30). If one out of two mixed gonads has carcinoma in situ it must be removed. If both gonads are affected – an alternative radiotherapy may be considered.

Discussion

Overlooking the wide variety of congenital genital anomalies it is obvious that the pathology is complex, diagnosis is difficult and in most situations a long treatment is required. The physicians are not always able to establish the diagnosis immediately after birth, especially if the external genitals appear normal or with a known pathology such as hypospadias or cryptorchidism. If the external genitalia have both female and male features then all necessary examinations and tests are carried on as early as possible.

Sometimes, when the family history is precisely collected, some of the genital anomalies could be suspected and the treatment could be applied prenatally, for example in case of AGS. In early infancy the children with genital anomalies should be managed by a specialist team including a pediatric surgeon, an endocrinologist and a genetician. Certain examinations and tests should be performed, such as: karyotyping, ultrasound of internal genitals, and if necessary CT and MRI, urine and blood tests for hormonal levels, and endoscopy before surgery. At the ultrasound examination it is important to look at the urinary tract because there are often associated anomalies there. When the specialist team makes a decision regarding the patient's sex based on the physiological, genetical and prognostic criteria, then the best time for surgery is decided too. In children sex reassignment is almost never undertaken unless the diagnosis is established early enough, usually during the first few months of life and if all possible changes are accepted by the family. In fact the sex of rearing depends on genetical and physiological criteria and on the prognosis of life quality in the future. In all other cases surgical and medical treatment is applied to emphasize or encourage the development of the appropriate sex features, trying to avoid anatomical discrepancy and helping to confirm psychological identity. Considering the importance of the prognostic criteria it is necessary to mention that the penile length and diameter should be measured. Although these parameters can vary, it is desirable for a full term neonate to have a penis of 3.5±0.4cm and 1 cm in diameter, while at the 35th gestational week it should be 3.0±0.4cm and at 30th gestational week – 2.5±0.4cm long. If the penis of a full term baby is shorter than 1.5×0.7 cm, then a change of sex might be considered. In this situation the response reaction to hCG stimulation might be helpful too (8).

Many pediatric surgeons recommend surgical treatment during the first 6 months after birth (7, 11, 18, 23). At that time the tissues are still very plastic and affected by the maternal estrogens, the healing is quicker and fewer repeated surgical procedures are required. But there is another attitude, especially popular in the USA, claiming that the ethical principles are

Table 3. **Data from surgical experience treating female congenital anomalies in overseas centers**

Center, investigators, publication data	Type of pathology	Number of patients	Age at the operation time	Follow-up	Type of surgery and following complications
Washington K. Newman et al., 1991	Various types of UGS	42	No data	1–24 years, mean. 8 years	Op.: clitoral reduction, vaginal pull-through, introitus opening, skin flap plasty, colonic replacement *8 vaginal stenosis out of 14patients (after pull-through), 2 cases of uncomfortable hair growth because of skin flaps*
Jerusalem A. Farkas et al., 2001	High UGS	44	0.9±0.3 years	4.7±2.6 years	Op.: 1-stage genitoplasty: TUM en block 1 – intraoperative rectal injury 3 – wound infections *No vaginal stenosis*
Indiana R. C. Rink et al, 1997	High UGS	8	6 months – 25 years	Up to 5 years	Op.: Perineal prone 1-stage approach 1 – urethrovaginal fistula (closed by itself) *No vaginal stenosis*
Minnesota R. Gonzales et al., 1990	High UGS	9	3 months – 12 years	Up to 2 years	Op.: 1-stage vaginal pull-through 2 – meatal stenosis 1 – low urethrovaginal fistula *No vaginal stenosis*
Boston H. Hendren et al., 1995	High UGS, Prader V°	16	10 months– 12 years	Up to31 years	Op.: pull-through, some performed "at early age" *3* – vaginal stenosis *6 – required secondary vaginoplasty*
Essen, K. H. Krege et al., 2000	UGS Prader II–V°	25	Ist stage at 3.6 years, if 2 stages– IInd at 10.4 years	Examined at 14–33 years	Op.: 24 Fortunoff flaps, 1 pull-through *9 vaginal stenosis out of 20 patients* – (after 1-stage procedure, Prader III–V°) 1 urethrovaginal fistula
Leeds, N. K. Alizai et al., 1999	No data	14	Mean 2.5 years	Examined at mean age 13.1 years	Op.: no data, except it was performed in "early infancy" *13 vaginal stenosis out of 14 (various degrees)* *6 persistent UGS (postoperatively)*

violated if any type of surgery is performed without the patient's (not parental) consent (4, 5). Contemporary medicine cannot present enough analyses of late results of genital surgery to prove the correctness of that attitude.

Mentioning surgical treatment the most common complication after vaginoplasty is vaginal stenosis at the site of anastomosis or urethrovaginal fistula. It is very important from the surgical point of view because some patients have to undergo repeated operations due to scaring complications. The data revealing surgical experience from different overseas centers is presented in table 3 (1, 6, 11, 13, 17, 19). The data does not suggest an advantage of certain surgical method but the clear tendency can be observed showing quite good results on close follow-up but revealing quite a significant rate of complications at puberty or later. Speaking about the intersex patients the statistical comparison is complicated because of anatomical peculiarities of each individual. Apparently it is not possible to avoid a certain degree of vaginal stenosis after the operation but it partially depends on the chosen surgical technique and experience of the surgeon. 7-14 days postoperatively a vaginal dilatation scheme is introduced, using special metal or plastic moulds (Hegar dilators). After urethroplasty in boys the most common complications again are fistulas or urethral stenosis. Because of those complications some patients must undergo several repair procedures.

The fertility problem is of great significance for the patients with genital anomalies. Theoretically all girls affected by AGS have a reproduction potential, because their genetical sex is 46XX and their internal genitalia are female. But in practice those girls develop quite many behavioral problems because of their exceptional status and life lasting treatment. Certain physiological problems such as disturbances of the menstrual cycle may occur; therefore a normal pregnancy is not always possible. But still these patients have better fertility prospects compared to other individuals with intersex anomalies (26).

Masculine infertility is also determined by several causes:

1. The testicles may need to be removed due to a malignant process.

2. If there is a rudimental vaginal utricle the prostate might be underdeveloped and this may lead to reduced semen ejaculation.

3. Normal sexual intercourse may not be possible due to an underdeveloped penis.

4. Primary oligospermia is common for the patients with partial androgen insensitivity.

We hope that the short review of congenital genital anomalies presented in this article gives the reader an understanding of the complexity of the pathology and the responsibility of the specialists involved in deciding the further life of a single individual patient.

Įgimtos lytinių organų anomalijos. Diagnostikos ir gydymo aspektai

Indrė Zaparackaitė, Vidmantas Barauskas
Kauno medicinos universiteto Vaikų chirurgijos klinika

Raktažodžiai: embriologija, Vulfo ir Miulerio takai, hermafroditizmas, gonadų disgenezė, urogenitalinis sinusas.

Santrauka. Įgimtos lytinių organų anomalijos yra labai sudėtinga patologija. Norint žinoti jų atsiradimo priežastis, ypač svarbu atkreipti dėmesį į genetinius bei embriologinius vystymosi ypatumus. Šiuos sutrikimus lemia skirtingi veiksniai, dažniausiai chromosomų patologija, endokrininiai pokyčiai ir biocheminių procesų sutrikimai. Sunkumų kyla tuomet, kai genetinė lytis neatitinka lytinių požymių. Tikrasis hermafroditizmas, įgimta antinksčių hiperplazija, testikulinė feminizacija, gonadų disgenezė – būdingiausi sindromai. Diagnostikos kriterijai panašūs (kariotipo nustatymas, hormonų ir jų apykaitos produktų ištyrimas, genitalijų echoskopija ir endoskopija, prireikus – radiologinis ištyrimas), bet medikamentinis ir chirurginis gydymai kiekvienam pacientui taikomi individualiai.

Adresas susirašinėjimui: I. Zaparackaitė, KMU Vaikų chirurgijos klinika, Eivenių 2, 3007 Kaunas

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