RISKS OF GONADAL MALIGNANCY AND REPRODUCTIVE PROGNOSIS IN INDIVIDUALS WITH CONGENITAL SEX DEVELOPMENT DISORDERS

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SUMMARY

The risk of gonadal malignancy varies according to the type of sex development disorder. It depends on the presence of the Y chromosome in the karyotype and the location of the gonads.

Aim of the study: Assessment of the risks of gonadal malignancy and reproductive prognosis in female phenotype patients with congenital disorders of sex development and Y chromosome in karyotype.

Materials and methods: 48 patients with female phenotype and congenital disorders of sex development, with detected Y chromosome in the karyotype (46, XY and 45,X/46,XY) were examined. All patients underwent clinical, gynecological, hormonal, and ultrasound examinations. In 32 cases, gonadectomy was performed. A Histomorphological study of excised gonads was carried out. Based on conducted examinations, a complete form of 46,XY gonadal dysgenesis (Swyer syndrome) was identified in 3 cases, in 2 cases – a partial form of gonadal dysgenesis with a background of the Turner syndrome phenotype. The complete form of androgen insensitivity syndrome (CAIS) was diagnosed in 33 cases, and a partial form of androgen insensitivity syndrome (PAIS) in patients with female phenotype – in 8 cases. In 2 cases, an ovotesticular disorder was established.

Results: Patients with complete and partial forms of gonadal dysgenesis with intra-abdominal localization of gonads, taking into account the high risk of malignancy, underwent gonadectomy immediately after diagnosis, regardless of age, to prevent malignancy. Subsequently, they were prescribed hormone therapy with estrogens and estrogen-gestagens. Despite the pessimistic reproductive prognosis in 2 cases, pregnancy and the birth of a healthy child was achieved with egg donation.

Keywords: Gonadal malignancy, Y chromosome, sex development disorder, gonadectomy, androgen insensitivity syndrome, reproductive prognosis, Swyer syndrome

Considering the low risk of gonadal malignancy in patients with CAIS, 25 patients underwent intra-abdominal testicular excision after the end of puberty and were prescribed monotherapy with estrogens. In one case, in a patient with CAIS at the age of 18, a seminoma of the intra-abdominal gonad has been detected, which is extremely rare. A 41-year-old patient with CAIS gonadoblastoma was diagnosed by histomorphological examination in the inguinal located gonad after gonadectomy.

In adolescent patients with female phenotype and PAIS with a high risk of gonadal malignancy, gonadectomy was performed immediately after diagnosis, regardless of gonadal localization, to prevent malignancy and to stop the masculinization effect. Subsequently, they were prescribed monotherapy with estrogens. Reproductive prognosis for patients with CAIS and PAIS is pessimistic, although it is possible to have a child using a male partner's sperm in a donor-surrogacy program.

Despite a low risk of malignancy in female phenotype patients with ovotesticular disorder and 46,XY karyotype underwent intra-abdominal gonadectomy as neither ovotestis nor contralateral testis contained structures usable for reproduction. Patient management and reproductive prognosis are similar to the CAIS in such cases.

Conclusions: Timely and correct diagnosis and management of congenital sex development disorders is the most reliable approach to gonadal malignancy prevention. After that, it is possible to select adequate methods of assisted reproductive technologies, which is reflected in the improvement of the quality of life of such individuals.

Timely diagnosis and optimal management of congenital sex development disorders (SDD) are essential not only for minimizing main complaints related to the reproductive system of patients (delayed sex development, amenorrhea, inadequate sexual development, infertility, etc.) but also for preventing such long-term complications as osteoporosis, cardiovascular diseases and in some cases increased risk gonadal malignancy.[1-7]

The risk of gonadal malignancy differs by type of SDD and depends on the presence of the Y chromosome in the karyotype and gonadal localization.[3,7,8]

Risks of gonadal malignancy by diagnoses and recommendations (Tab. 1)

Risk group	Disease	Risk of malignancy (%)	Recommendation
High	Complete and partial forms of gonadal dysgenesis (+Y), with intra-abdominal localization of gonads	15-35	Gonadectomy immediately after diagnosis
	Partial forms of androgen insensitivity syndrome with non-scrotal gonads	50	Gonadectomy immediately after diagnosis
Average	Turner syndrome (+Y)	12	Gonadectomy immediately after diagnosis
	Partial forms of androgen insensitivity syndrome with scrotal gonads	Unknown	Biopsy and radiological investigation
Low	Complete form of androgen insensitivity syndrome	2	Biopsy and radiological investigation
	Ovotesticular SDD	3	Excision of testicular tissue?
	Turner syndrome (-Y)	1	No

AIM OF THE STUDY

Assessment of the risks of gonadal malignancy and reproductive prognosis in female phenotype patients with congenital SDD and Y chromosome in the karyotype.

MATERIALS AND METHODS

48 patients with female phenotypes and congenital sex development disorders were examined. A Y chromosome was detected in the karyotype (46, XY and 45, X/46, XY).

All patients underwent clinical, gynecological, hormonal, and ultrasound examinations. In 32 cases, gonadectomy was performed. Histomorphological study of excised gonads was carried out. Based on conducted examinations, a complete form of 46, XY gonadal dysgenesis (Swyer syndrome) was identified in 3 cases, in two instances – a partial form of gonadal dysgenesis with a background of the Turner syndrome phenotype. The complete form of androgen insensitivity syndrome (CAIS) was diagnosed in 33 cases, and a partial form of androgen insensitivity syndrome (PAIS) in patients with female phenotype – in 8 cases. In 2 cases, an ovotesticular disorder was established.

ETHICAL CONSIDERATIONS

All the adult participants and parents of adolescent individuals signed a written consent form.

RESULTS AND DISCUSSION

Among the patients with SDD under our observation, three were diagnosed with Swyer syndrome (a complete form of gonadal dysgenesis). The patients' ages corresponded to 15, 19, and 24.

All three patients were of the female phenotype and were of average height. No somatic anomalies or visceropathies were observed. In all cases, clinical and hormonal features characteristic of hypogonadotropic hypogonadism were established. The karyotype in all three cases was 46, XY in peripheral blood lymphocyte culture.

Considering that the risk of gonadal malignancy in the complete form of 46, XY gonadal dysgenesis is high (15-35%), all three patients underwent gonadectomy immediately after the diagnosis.[9,10,11] By histomorphological study, streak gonads were represented by connective tissue. In one case, epithelial cells of Leydig cell type were detected. After gonadectomy, patients were prescribed hormone therapy with estrogens and estrogen-gestagens, as well as vitamin D and calcium preparations. As a result of the treatment, patients showed secondary sexual characteristics and an enlarged uterus. After treatment, two patients became pregnant using egg donation, carried the pregnancy to term, and gave birth to a healthy child. One patient chose to adopt a child.

Among the patients examined, two adolescents (15 and 16 years old) had Turner's phenotype (height 138 and 141 cm), visceropathies were detected in no case, both patients had clinical and laboratory characteristics of hypergonadotropic hypogonadism. They had hairiness on the pubic area, and the clitoris was not sharply hyperplastic. Ultrasonographic examination revealed a streak uterus and unilateral streak gonad; on the other side, a gonad without follicles. In both cases, the karyotype was mosaic 45, X /46, and XY.

A diagnosis of mixed, partial gonadal dysgenesis was made. In such cases, taking into account the increased risk of gonadal malignancy and current recommendations, laparoscopic bilateral gonadectomy was performed.[3,9,12] By histomorphological study, streak gonads were represented by connective tissue structures, gonads on the other side – with dysgenetic testicles. Clitorectomy was performed in both cases. After surgery, hormone therapy with estrogens and estrogen-gestagens, vitamin D, and calcium preparations were prescribed. On the background of hormone therapy, mamae growth was noted, and the uterus also grew. One patient tried to become pregnant through in vitro fertilization using an egg donation program after becoming sexually active, but two attempts were unsuccessful.

In both complete and partial forms of gonadal dysgenesis, taking into account the high risk of gonadal malignancy, gonadectomy is performed immediately after the diagnosis is made, and therefore the reproductive prognosis is pessimistic. However, in such cases, it is possible to achieve pregnancy and have a child using egg donation programs.[7,13]

Therefore, it is essential to diagnose those forms of SDD in time that are characterized by a high risk of gonadal malignancy in time so that a gonadectomy can be performed to prevent malignancy and hormone replacement therapy can be performed after the gonadectomy.

33 patients (12-28 years old) were diagnosed with a complete form of androgen insensitivity syndrome (CAIS), and eight patients (14-16 years old) with female phenotype were diagnosed with a partial form of androgen insensitivity syndrome (PAIS).

Patients with CAIS had female phenotype, female passport gender and psychosexual orientation, well-developed mamae, sparse pubic hair, female-type external genitalia without clitoromegaly, and short, blind-ending vagina.

Ultrasonography did not detect the uterus. Gonads of different localizations were detected (localized intra-abdominally, inguinally, or at the thickness of the labia majora).

In all cases, hormonal parameters were typical for males, and the karyotype was consistent with the 46, XY male norm. Considering that the risk of gonadal malignancy in CAIS cases is low, patients with intra-abdominal and inguinal localizations underwent gonadectomy after puberty was completed. Besides, it is known that the risk of malignancy increases with age.[8,14]

One of our patients with CAIS, at the age of 41, was diagnosed with gonadoblastoma by histological study after inguinal testis resection.

According to literature data,[1] some patients with CAIS report a decrease in libido after gonadectomy. No changes in sexual function were detected after gonadectomy in patients under our observation. One patient postponed orchiectomy because she had good sexual penile-vaginal contact with a man, with frequent orgasms, and feared that orchiectomy would negatively affect her sexual life.

All patients with CAIS after gonadectomy were prescribed monotherapy with estrogens, vitamin D, and calcium preparations. Despite the low risk of gonadal malignancy in CAIS cases, one 18-year-old adolescent patient with CAIS was diagnosed with seminoma in intra-abdominally localized left testis, which is considered a rare case.[15]

Thus, despite the low risk of gonadal malignancy in patients with CAIS, considering rare cases, it is advisable to monitor intra-abdominally localized testes from the puberty period. 76

All patients with PAIS[8], who were assessed as girls with female psychosexual disposition, were referred to us due to revealing the signs of masculinization during adolescence. As soon as the diagnosis was made, regardless of the location of gonads, all our adolescent individuals underwent bilateral orchiectomy according to the protocol to stop the progression of masculinization and considering that in the cases of PAIS, the risk of testicular malignancy is increased (50%).[1,8] These individuals underwent feminizing genitoplasty and were prescribed estrogen replacement therapy. After 1-year follow-up, an increase in mamme, change in tone of voice, and improvement in mood were found in these individuals.

Reproductive prognosis in both CAIS and PAIS patients assessed as girls is pessimistic. As a way to have a child, these patients can consider joining a donation-surrogacy program using the male partner's sperm or adopting a child.

Among our patients with SDD 46, XY ovotesticular disorder was detected in two patients (17 and 35 years old) with female phenotype. The diagnosis was confirmed by laparoscopic biopsy and histomorphological examination of gonads after gonadectomy through the establishment of unilateral ovotestis. In both cases, hypoplastic testicular tissue with clearly manifested fibrosis was detected in the gonad on the other side. A 35-year-old patient with 46, XY ovotesticular SDD was married to a man and referred us due to infertility.

Although the risk of ovotestis malignancy is relatively low (3%),[3,9] in these patients with 46, XY karyotype structurally incomplete uterus in the form of Müllerian derivatives and the presence of dysgenetic testicle on one side and hypoplastic testicular tissue in the ovotesticle on the other side due to absence of reproductive potential, it was advisable to perform gonadectomy after obtaining patient's informed consent. After surgery, patients were prescribed hormone replacement therapy with estrogen.

It is impossible to consider ovotesticular disorder as a single syndrome because there is no typical phenotype or karyotype characteristic for it. Thus, the presence of ovotestis is a determinant in diagnosis, which is established only by histomorphological study. Phenotypes may differ: feminine, ambisexual, or masculine.[3,7,16]

Reproductive prognosis: most often pessimistic due to incomplete development of the Müllerian ducts (uterus, fallopian tubes, upper two-thirds of the vagina) and gonadal tissue, as well as the need to perform gonadectomy. However, taking into account the development of modern reproductive technologies in the recent period, in individual cases, it is possible to consider the expediency of cryopreservation of reproductive materials before gonadectomy. It is known that in ovotesticular disorders, ovulation is observed in 50% of cases. Pregnancy and even delivery have been described in such patients, suggesting that there may be normal development of both female-type external and internal genitalia, even in the cases of 46, XY ovotesticular disorder.[17]

The literature describes 12 cases of spontaneous pregnancy in patients with 46, XX ovotesticular SDD with a female phenotype.[16] Only one case of fertility in a 46 XY patient has been described. In all those cases, surgical excision of testicular tissue was performed before pregnancy. In such patients, excision of androgen-producing testicular tissue may improve ovulation.[17]

One of our patients with the ovotesticular disorder and female phenotype with 46, XX karyotype was diagnosed by diagnostic laparoscopy and gonadal biopsy, having an ovary on one side

and 77 ovotestes on the other side with signs of ovulation. Taking into account the patient's desire, it was planned to cryopreserve the eggs and subsequently use them in the surrogacy program, as the patient did not have a uterus, and only Müllerian derivatives were presented. Müllerian derivatives were excised during surgery.

Thus, in the cases of ovotesticular disorders, the reproductive prognosis is sharply different – from pessimistic to favorable and a solution to the issue of gonadectomy requires an individual approach, taking into account reproductive potential and the anatomy of the genitals.

CONCLUSION

- In patients with complete and partial forms of gonadal dysgenesis, in the presence of Y chromosome in the karyotype, taking into account the high risk of gonadal malignancy, gonadectomy should be performed immediately after diagnosis. After gonadectomy, it is possible to achieve pregnancy using egg donation on the background of estrogen-gestagen replacement hormone therapy.
- Despite the low risk of gonadal malignancy in complete forms of androgen insensitivity syndrome, it is advisable to monitor the gonads from puberty and, based on this, to plan gonadectomy in the postpubertal period and then monotherapy with estrogens. Reproductive prognosis is pessimistic, although it is possible to have a child using a male partner's sperm through surrogacy-donation programs.
- In partial forms of androgen insensitivity syndrome, gonadectomy in patients with a female passport gender and psychosexual disposition should be performed immediately after the diagnosis is made, considering the high risk of malignancy and to prevent the progression of masculinization in any location of the gonads. Feminizing genitoplastic surgery and estrogen replacement therapy are necessary to achieve feminization, improve quality of life, and prevent long-term complications. Reproductive prognosis is similar to complete forms of androgen insensitivity syndrome.
- Considering the low risk of ovotesticular malignancy in case of ovotesticular disorders, it is possible to preserve it and, if possible, cryopreserve eggs for later use in assisted reproductive technology (ART) programs. Excision of the testicle on the other side increases the chances of ovulation in the ovotestis. Comprehensive clinical polymorphism of patients with ovotesticular disorders requires an individualized approach in selecting the type of assisted reproductive technology, taking into account the anatomy of the gonads and internal genital organs.

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