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POREMEĆAJI POLNE DIFERENCIJACIJE: ISKUSTVO TERCIJERNOG CENTRA

Snježana Mijatović[1], Tatjana Milenković[2], Katarina Sedlecki[2], Vladimir Kojović[1,2], Predrag Ilić[1,2], Jelena Martić[1,2], Katarina Mitrović[1,2], Slađana Todorović[2], Marko Marjanović[2], Jovana Tončev[2], Sanja Panić-Zarić[2], Rade Vuković[1,2*]

[1] Medicinski fakultet Univerziteta u Beogradu, Beograd, Republika Srbija
[2] Institut za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić", Beograd, Republika Srbija

SAŽETAK

Uvod/cilj: Poremećaji polne diferencijacije (PPD) obuhvataju heterogenu grupu urođenih stanja kod kojih postoji neusklađenost hromozomskog pola, gonadnog pola i izgleda spoljašnjih genitalija. Učestalost PPD-a iznosi 1 na 4.500-5.500 novorođene dece godišnje. Kongenitalna adrenalna hiperplazija (KAH) usled deficita enzima 21-hidroksilaze predstavlja jedan od najčešćih i najbolje poznatih uzroka PPD. Ostale forme KAH-a, kao i drugi uzroci PPD-a, se javljaju sa značajno manjom pojedinačnom učestalošću i samim time predstavljaju daleko veći dijagnostički i terapijski izazov. Cilj istraživanja bila je analiza etiologije i kliničkih karakteristika PPD-a, kao i promena u dijagnostičkom i terapijskom pristupu PPD-u, u tercijernom centru tokom prethodnih 13 godina.
Metode: Istraživanje je sprovedeno po tipu retrospektivne kohortne studije kojom su bili obuhvaćeni svi pacijenti ispitivani zbog PPD-a, a koji su dijagnostikovani u Službi za endokrinologiju Instituta za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić" u periodu od decembra 2007. godine do novembra 2020. godine. U istraživanje nisu uključena deca sa PPD-om kod kojih je utvrđena dijagnoza KAH usled deficita 21-hidroksilaze.
Rezultati: Studijom je obuhvaćeno 31 dete sa PPD-om i to 24 (77%) dece imalo je 46XY PPD, 3 (10%) 46XX PPD, a 4 (13%) hromozomski PPD. Definitivna dijagnoza je postavljena kod 25 dece (81%), a najčešća etiologija PPD-a je bila gonadna disgenezija (55%), zatim sindrom neosetljivosti na androgene (10%) i atipične forme KAH-a (7%). U periodu 2016-2020. godine (period 2) ispitivano je 18 dece sa PPD-om, a 13 dece u periodu 2007-2015. godine (period 1). Specifična dijagnoza etiologije PPD-a je utvrđena kod većeg broja dece (89%) u periodu 2 u odnosu na period 1 (69%). Takođe, tokom perioda 2 genitalna hirurgija je učinjena kod značajno manjeg broja dece (11%) i u starijem uzrastu (prosečan uzrast 6,8 godina) nego u periodu 1 (64%, p <0,05; prosečan uzrast 4,8 godina).
Zaključak: Tokom kasnijeg perioda uočava se povećanje broja ispitivane dece, kao i procenat PPD-a sa utvrđenom etiologijom. Takođe, dijagnoza se sve češće postavlja na osnovu genetskih analiza, a genitoplastika se sprovodi kod sve manjeg broja dece i u kasnijem uzrastu. Deca sa PPD-om zahtevaju holistički i multidisciplinarni pristup radi što preciznije evaluacije pacijenata i pružanja adekvatnog i individualizovanog tretmana i nege.

Ključne reči: poremećaji polne diferencijacije, kongenitalna adrenalna hiperplazija, gonadna disgenezija, sindrom neosetljivosti na androgene

Uvod

Poremećaji polne diferencijacije (PPD), odnosno različitosti u polnoj diferencijaciji, obuhvataju klinički i patofiziološki heterogenu grupu stanja koja se najčešće manifestuju na rođenju u vidu ambivalentnog izgleda spoljašnjih genitalija ili u adolescentnom periodu u vidu izmenjenog razvoja sekundarnih polnih karakteristika. Poremećaji polne diferencijacije javljaju se sa učestalošću od 1:4.500-5.500 novorođene dece godišnje (1,2). Kod ovih pacijenata postoje odstupanja u fiziološkom razvoju hromozomskog, gonadnog ili fenotipskog pola (3,4).

Determinacija i diferencijacija pola su složeni procesi koji se odvijaju tokom prenatalnog perioda, a zatim se nastavljaju u postnatalnom periodu sve do sticanja polne zrelosti tokom puberteta i

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DISORDERS/DIFFERENCES OF SEX DEVELOPMENT: TERTIARY CENTRE EXPERIENCE

Snjezana Mijatovic[1], Tatjana Milenkovic[2], Katarina Sedlecki[2], Vladimir Kojovic[1,2], Predrag Ilic[1,2], Jelena Martic[1,2], Katarina Mitrovic[1,2], Sladjana Todorovic[2], Marko Marjanovic[2], Jovana Toncev[2], Sanja Panic-Zaric[2], Rade Vukovic[1,2*]

[1] School of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[2] Mother and Child Health Care Institute of Serbia „Dr Vukan Cupic", Belgrade, Republic of Serbia

SUMMARY

Introduction/aim: Disorders of sex development (DSD) comprise a heterogeneous group of congenital conditions with a difference between chromosomal, gonadal sex and the appearance of the external genitalia. The frequency of DSD is 1: 4,500-5,500 newborns per year. Congenital adrenal hyperplasia (CAH) due to the deficiency of the 21-hydroxylase enzyme is one of the most common and best-known causes of DSD. Other forms of CAH, as well as other causes of DSD, occur with significantly lower individual frequencies and are thus more challenging to diagnose and treat. The aim of the study was to analyse the etiology and clinical characteristics of DSD, as well as changes in the diagnostic and therapeutic approach to DSD in the tertiary center during the previous 13 years.
Methods: The study was conducted in the form of a retrospective cohort study which included all patients investigated for DSD at the Department of Endocrinology of Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic" during the period from December 2007 until November 2020. Children with DSD caused by CAH due to 21-hydroxylase deficiency were not included in this study.
Results: The study included a total of 31 children with DSD: 24 children (77%) had 46XY DSD, 3 (10%) had 46XX DSD, and 4 children (13%) had chromosomal DSD. A definitive diagnosis of specific etiology has been made in 25 children (81%), and the most common etiology of DSD was gonadal dysgenesis (55%), followed by the androgen insensitivity syndrome (10%) and atypical forms of CAH (7%). During the period 2 (2016-2020) more children with DSD (n = 18) were examined compared to the period 1 (2007-2015) and the specific etiological diagnosis was established in a larger number of children with DSD (89%) compared to the period 1 (69%). Also, during period 2 (2016-2020) genital surgery was performed in a significantly lesser number of children (11%) and at a later age (average age 6.8 years) than in period 1 (64%, average age 4.8 years; $p < 0.05$).
Conclusion: During the latter period (2016-2020), there has been an increase in the number of investigated children as well as the percentage of DSD with established specific etiology. Also, the diagnosis is increasingly being made on the basis of genetic analysis, and genitoplasty is performed in a decreasing number of children and at a later age. A holistic and multidisciplinary approach is required for the evaluation treatment of children with DSD.

Keywords: disorders of sex development, differences of sex development, congenital adrenal hyperplasia, gonadal dysgenesis, androgen insensitivity syndrome.

Introduction

Disorders of sex development (DSD), that is, differences of sex development encompass a heterogeneous group of conditions with diverse clinical features and pathophysiology that are manifested at birth as ambiguous external genitalia and in adolescence as changes in the development of secondary sexual characteristics. The frequency of disorders of sex development is 1: 4,500-5500 newborns per year (1,2). In these patients, deviations in the physiological development of chromosomal, gonadal and phenotypic sex occur (3,4).

Sex determination and differentiation are complex processes that evolve during the prenatal period, and then continue in the postnatal period until sexual maturation during puberty and adolescence. During fertilization, male and female

adolescencije. Prilikom oplođenja spajaju se muški i ženski gameti, i nastaje zigot, pri čemu dolazi do determinacije *hromozomskog (genetskog) pola*, odnosno do nastanka ploda koji je najčešće uobičajenog ženskog (46,XX) ili muškog (46,XY) kariotipa. Hromozomski pol ima glavnu ulogu u diferencijaciji primordijalne gonade u muške (testis) ili u ženske (ovarijumi) gonade, što označava *gonadni pol*. *Fenotipski pol* se poslednji diferencira i podrazumeva uspostavljanje razlika u izgledu i građi između muških i ženskih unutrašnjih i spoljašnjih genitalija. Sticanje muškog ili ženskog fenotipskog pola odvija se tokom prenatalnog i postnatalog perioda pod uticajem muških, odnosno ženskih polnih hormona koji se luče iz gonada. Odstupanje u nekom od ovih procesa vodi ka nastanku poremećaja u diferencijaciji pola, što se može manifestovati spektrom različitih kliničkih nalaza kroz različite faze rasta i razvoja deteta (1-4).

Postoje brojne podele poremećaja polne diferencijacije, a jedna od najčešće korišćenih u kliničkoj praksi je podela na osnovu nalaza kariotipa. Na ovaj način se svi poremećaji polne diferencijacije mogu podeliti na: 46,XY PPD, 46,XX PPD i hromozomske PPD (Tabela 1). Jedan od najznačajnijih uzroka PPD je kongenitalna adrenalna hiperplazija (KAH), kao najčešći uzrok PPD kod dece sa 46,XX kariotipom (1,3,5). Ostale forme KAH-a, kao i drugi uzroci PPD-a, se javljaju sa značajno manjom pojedinačnom učestalošću i samim time predstavljaju daleko veći dijagnostički i terapijski izazov. Zbog vrlo složenog dijagnostičkog i terapijskog pristupa, kod dece sa PPD-om neophodno je učešće multidisciplinarnog tima specijalista, koji sačinjavaju brojni specijalisti, najčešće neonatolog, pedijatrijski endokrinolog i urolog, ginekolog, radiolog i psihijatar (4,6).

Cilj ovog istraživanja bio je pregled etiologije i kliničkih karakteristika PPD-a, kao i promena u dijagnostičkom i terapijskom pristupu PPD-u, u tercijernom centru tokom prethodnih 13 godina.

Metode

Istraživanje je sprovedeno po tipu retrospektivne kohortne studije kojom su obuhvaćeni pacijenti ispitivani zbog PPD-a, a koji su se javili Službi za endokrinologiju Instituta za zdravstvenu zaštitu majke i deteta „Dr Vukan Čupić“ (IMD) u periodu od decembra 2007. godine do novembra 2020. godine. U istraživanje nisu uključena deca sa potvrđenom dijagnozom KAH-a usled deficita 21-hidroksilaze, a uključena su sva ostala deca sa PPD-om kod kojih je utvrđena bilo koja druga etiologija: gonadna disgenezija, sindrom rezistencije na androgene, atipični oblici KAH-a i drugi poremećaji steroidogeneze, kao i pacijenti kod kojih nije utvrđena etiologija PPD-a.

Iz medicinske dokumentacije Službe za endokrinologiju IMD-a prikupljeni su osnovni demografski podaci o pacijentima (pol dodeljen na rođenju, uzrast), podaci o razlogu javljanja lekaru i uzrastu u kojem su se pacijenti, odnosno roditelji, javili zbog neke od manifestacija PPD-a, podaci o grupi PPD-a, porodičnoj anamnezi, podaci o postavljenim specifičnim dijagnozama etiologije PPD-a na osnovu sprovedenih dijagnostičkih postupaka, uključujući analizu kariotipa i hormona, biopsiju gonada i vizualizacione dijagnostičke metode (ultrazvučni - UZ i preged magnetnom rezonancom - MR). Takođe su prikupljeni podaci o utvrđenoj dijagnozi, podaci o postojanju pridruženih anomalija, kao i podaci o sprovedenoj hormonskoj i hirurškoj terapiji pacijenata, kao i o datom savetu za podizanje deteta u određenom polu. Za sve pacijente su prikupljeni podaci o izgledu spoljašnjih genitalija koji su zatim kvantitativno analizirani korišćenjem skora izgleda spoljašnjih genitalija (engl. *External genitalia score* - EGS) (7).

U cilju analize promena u dijagnostičkom i terapijskom pristupu PPD-u tokom ukupnog perioda posmatranja od 13 godina, pacijenti su, u zavisnosti od godine u kojoj su zbog PPD-a ispitivani u IMD-u podeljeni u dve grupe: period 1 (pacijenti koji su se javili lekaru u periodu od 2007. godine do 2015. godine) i period 2 (pacijenti koji su se javili lekaru u periodu od 2016. godine do 2020. godine).

Statistička obrada prikupljenih podataka izvršena je u programu SPSS, metodama deskriptivne i analitčke statistike (*Hi-kvadrat test* i *Mann-Witney U test*). Prikupljeni podaci o pacijentima su upoređivani u odnosu na period ispitivajna u IMD-u, kao i u odnosu na grupu PPD-a (46XY PPD, 46XX PPD i hromozomski PPD). Rezultati su prikazani kao apsolutni brojevi (%), odnosno kao aritmetička sredina ± standardna devijacija, sa rasponom ekstremnih vrednosti u zagradi. Statistički značajnim rezultatima smatrani su rezultati kod kojih je p vrednost iznosila manje od 0,05.

gametes unite to form a zygote, resulting in chromosomal (genetic) sex determination, that is, the development of fetus with the most common karyotypes for females (46, XX) or males (46, XY). Chromosomal sex has a key role in the differentiation of the primordial gonad into male (testes) or female (ovaries) gonads, which is gonadal sex. Phenotypic sex differentiates last and it refers to differences in the appearance and structure of male and female internal and external genitalia. The development of male or female phenotypic sex occurs during the prenatal and postnatal period under the influence of male or female sexual hormones secreted by the gonads. Deviations of some of these processes lead to disorders of sex development, which may be manifested by a range of diverse clinical findings during different stages of children's growth and development (1-4).

There are numerous classifications of disorders of sex development, and one of the most frequently used in the clinical practice is the classification according to the karyotype findings. Thus, all disorders of sex development can be classified into: 46,XY DSD, 46,XX DSD and chromosomal DSD (Table 1). One of the most significant causes of DSD is congenital adrenal hyperplasia (CAH), as the most common DSD in children with 46,XX karyotype (1,3,5). Other forms of CAH, as well as other causes of DSD, occur with significantly lower individual frequency and are, therefore, more challenging to diagnose and treat. Due to a very complex diagnostic and therapeutic approach, in children with DSD a multidisciplinary team of specialists should necessarily be involved, including numerous specialists, most frequently neonatologists, pediatric endocrinologists and urologists, gynecologists, radiologists and psychiatrists (4,6).

The aim of this study was to analyze the etiology and clinical characteristics of DSD, as well as changes in the diagnostic and therapeutic approach to DSD in the tertiary center during the previous 13 years.

Methods

The study was conducted as a retrospective cohort study, which included all patients that were examined due to DSD at the Department of Endocrinology of Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic" from December 2007 to November 2020. Children with the confirmed diagnosis of CAH due to the deficiency of 21-hydroxylase were not included in the study, while all the other children with DSD of different etiology were included in the study, including gonadal dysgenesis, androgen insensitivity syndrome, atypical forms of CAH and other disorders of steroidogenesis, as well as patients without established etiology of DSD.

Basic demographic data about patients (sex attributed at birth, age) were collected from the medical documentation of the Department of Endocrinology of Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic", as well as data about reasons for visiting the doctor and age at which patients, that is, their parents visited the doctor due to some of the manifestations of DSD, data about DSD group, family anamnesis, data about specific etiology of DSD according to performed diagnostic procedures, including the analysis of karyotype and hormones, biopsy of gonads and visualization diagnostic methods (ultrasound and MR imaging). Also, data about the established diagnosis were collected, as well as data about the existence of comorbid anomalies, and data about the hormonal and surgical therapy, and the advice how to bring up a child of certain sex. Data about the appearance of external genitalia were collected for all patients, followed by quantitative analysis which was done with the help of external genitalia score (EGS) (7).

In order to analyze changes in the diagnostic and therapeutic approach to DSD during the whole period of observation that lasted 13 years, patients were divided into two groups depending on the year when they were examined due to DSD at Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic": period 1 (patients who visited their doctor from 2007 to 2015) and period 2 (patients who visited their doctor during the period 2016-2020).

The statistical analysis of collected data was done with the help of SPSS program, using the methods of descriptive and analytical statistics (Chi-squared test and Mann-Whitney test). Collected data were compared in relation to the period of examination at the Institute, as well as in relation to the group of DSD (46 XY DSD, 46XX DSD and chromosomal DSD). The results were presented as absolute numbers (%), that is, as arithmetic mean ± standard deviation, with a range of extreme values in the brackets. The results were considered statistically significant if the p value was less than 0.05.

Rezultati

Tokom celokupnog perioda ovog istraživanja (2007-2020. godine) u našem centru je ispitano 31 dete sa PPD-om (uz isključivanje dece sa KAH-om usled deficita 21-hidroksilaze). Najveći broj (n=24, 77%) dece imao je 46XY PPD, troje (10%) 46XX PPD i 4 (13%) hromozomski PPD (Tabela 2). Uzrast u trenutku ispitivanja zbog PPD-a je najčešće bio neonatalni period (n=22, 71%), a najčešći razlog ispitivanja je bio ambivalentni izgled spoljašnjih genitalija (n=20, 64%) ili nepodudarnost nalaza prenatalnog/postnatalnog kariotipa sa izgledom spoljašnjih genitalija na rođenju (n=4, 13%), kao što je prikazano u Tabeli 2. Definitivna etiološka dijagnoza PPD-a je postavljena kod 25 dece (81%), a najčešća dijagnoza je bila gonadna disgenezija (n=17, 55%). Hormonska terapija je bila indikovana kod 10 dece (32%), genitalna hirurgija je učinjena kod 9 (31%), a gonadektomija kod 7 (23%). Klinički i laboratorijski podaci o ispitanicima, podaci dobijeni vizualizacionim dijagnostičkim metodama (UZ i MR) i podaci iz anamneze koji su od značaja u evaluaciji nastanka PPD-a prikazani su u Tabeli 2.

Od ukupnog broja dece sa PPD-om, 13 (41,9%) je ispitivano u IMD-u u periodu 1 (2007-2015), a 18 (58,1%) u periodu 2 (2016-2020). Karakteristike pacijenata u pogledu fizikalnog, laboratorijskog, UZ i MR nalaza, kao i sprovedenog lečenja, u zavisnosti od perioda javljanja i ispitivanja u IMD-u, prikazane su u Tabeli 3. Definitivna dijagnoza postavljena je u većem procentu kod dece koja su se javila zbog PPD-a u periodu 2 (n=16; 89%), u odnosu na decu koja su se javila u periodu 1 (n=9; 69%) (p=0,208). Veći broj dijagnoza potvrđen je hormonskim analizama kod pacijenata koji su se javili u periodu 2 (n=15; 83%), u odnosu na broj potvrđenih dijagnoza hormonskim analizama u periodu 1 (n=5; 38%) ($p < 0,05$, Tabela 3). Genitalna hirurgija se u periodu 2 sprovodila statistički značajno manje često (n=2; 11%) nego u periodu 1 (n=7; 64%) ($p<0,05$). Uzrast dece u trenutku sprovođenja prve genitalne hirurgije bio je viši u periodu 2 (6,8 godina) nego u periodu 1 (4,8 godina), kao što je prikazano u Tabeli 3.

Grupe PPD-a (46XY PPD, 46XX PPD i hromozomski PPD) razlikovale su se u odnosu na zastupljenost pojedinih tipova gonadne disgenezije (Tabela 4). Gonadna disgenezija bila je uzrok PPD-a kod 50% dece sa 46XY PPD-om, 33,3% dece sa 46XX PPD-om i kod sve dece sa hromozomskim PPD-om, odnosno mešovitom gonadnom disgenezijom (MGD). Kod 46XY grupe PPD-a najzastupljenija (58,3%) je bila parcijalna gonadna disgenezija (PGD), dok je u 46XX grupi PPD-a jedno dete sa gonadnom dis-

Tabela 1. Klasifikacija poremećaja polne diferencijacije (PPD) u zavisnosti od kariotipa (18)

46XY PPD	46XX PPD	Hromozomski PPD
Gonadna disgenezija (potpuna ili parcijalna)	Gonadna disgenezija	Mešovita gonadna disgenezija (45X/46XY i 46XX/46XY)
Ovotestikularni PPD	(Ovo)testikularni PPD	Varijante Tarnerovog sindroma
Poremećaji sinteze androgena (izolovani ili u sklopu atipičnih oblika KAH)	KAH, tipična forma (deficit 21-hidroksilaze)	Varijante Klinefelterovog sindroma
Sindrom potpune ili parcijalne neosetljivosti na androgene	KAH, atipične forme (deficit 11β-hidroksilaze, 17α-hidroksilaze, 3β-hidroksisteroid dehidrogenaze)	
Sindrom perzistentnih *Muller*-ovih kanala	Deficit placentalne aromataze	
Sindromske forme 46XY PPD (Smith-Lemli-Opitz, Denys-Drash, itd.)	Maternalni androgen-produkujući tumor	
	Uticaj egzogenih androgena (lekovi sa virilizujućim dejstvom)	
	Virilizujući luteom u trudnoći	
	Sindromske forme 46XX PPD	

PPD- poremećajima polne diferencijacije, KAH – kongenitalna adrenalna hiperplazija

Results

During the whole period of this study (2007-2020), 31 children with DSD were examined at the centre (with the exclusion of children with CAH caused by 21-hydroxylase deficiency). The largest number of children (n=24, 77%) had 46XY DSD, 3 children (10%) had 46XX DSD and 4 children (13%) had chromosomal DSD (Table 2). Age at the moment of examination due to DSD was most frequently the neonatal period (n=22, 71%), while the commonest reason for the examination was the ambiguous appearance of external genitalia at birth (n=20, 64%) or the incongruity between the analysis of prenatal/postnatal karyotype and the appearance of external genitalia at birth (n=4, 13%), as shown in Table 2. A definitive diagnosis of specific etiology was made in 25 children (81%), while the most common diagnosis was gonadal dysgenesis (n=17, 55%). Hormonal therapy was advised in 10 children (32%), while genital surgery was performed in 9 children (31%) and gonadectomy in 7 (23%). Clinical and laboratory data about examinees, data obtained with the help of visualization diagnostic methods (ultrasound and MR imaging) and data from anamnesis that were significant for the evaluation of DSD appearance are shown in Table 2.

Of the total number of children with DSD, 13 (41.9%) were examined at Mother and Child Health Care Institute during the first period (2007-2015), while 18 (58.1%) were examined in the second period (2016-2020). The characteristics of patients regarding the physical, laboratory, ultrasound and MR findings, as well as the performed treatment, depending on the period of visits and examination at the Institute, are shown in Table 3. A definitive diagnosis was established in a larger number of children who came to the doctor due to DSD during the second period (n=16, 89%), in comparison to children who visited the doctor during the first period (n=9, 69%) (p=0.208). Larger number of diagnoses was confirmed by hormonal analyses in patients during the second period (n=15, 83%) in comparison to the confirmed diagnoses using hormonal analyses in the first period (n=5, 38%) (p<0.05, Table 3). Genital surgery was performed less often during the second period and it was statistically significant (n=2, 11%) in comparison to the first period (n=7, 64%) (p<0.05). Also, during the second period, the first genital surgery was performed at a later age (6.8 years) than in the first period (4.8 years), as shown in Table 3.

Groups of DSD (46XY DSD, 46XX DSD and chromosomal DSD) were different depending on

Table 1. Disorders of sex development (DSD) depending on karyotype

46XY DSD	46XX DSD	Chromosomal DSD
Gonadal dysgenesis (complete or partial)	Gonadal dysgenesis	Mixed gonadal dysgenesis (45X/46XY i 46XX/46XY)
Ovotesticular DSD*	(Ovo)testicular DSD	Variants of Turner syndrome
Disorders of androgen synthesis (isolated or related to nonclassical types of CAH)	CAH, classic type (21-hydroxylase deficiency)	Variants of Klinefelter syndrome
Complete or partial androgen insensitivity syndrome	CAH. nonclassical types (11β-hydroxylase deficiency, 17α-hydroxylase deficiency, 3β hydroxysteroid dehydrogenase deficiency)	
Persistent Müllerian duct syndrome	Placental aromatase deficiency	
Syndrome forms of 46XY DSD (Smith-Lemli-Opitz, Denys-Drash, etc.)	Maternal androgen-producing tumor	
	Influence of exogenous androgens (drugs with virilizing effect)	
	Virilizing luteoma in pregnancy	
	Syndrome forms of 46XX DSD	

DSD-disorders of sex development, CAH-congenital adrenal hyperplasia

genezijom (GD) imalo *De la Chapell*-ov sindrom. Genitalna hirurgija je u većem procentu rađena kod dece sa hromozomskim PPD-om (kod 75,0% ove dece) i kod dece sa 46XX PPD (66,7%), dok je genitalnoj hirurgiji podrvgnuto znatno manje dece sa 46XY PPD (18,2%) ($p<0,05$). Karakteristike pacijenata u pogledu fizikalnog, laboratorijskog, UZ i MR nalaza, kao i sprovedenog lečenja, u zavisnosti od grupe PPD-a, prikazane su u Tabeli 4.

Diskusija

Poremećaji polne diferencijacije (PPD), odnosno različitosti u polnoj diferencijaciji, obuhvataju spektar kongenitalnih stanja kod kojih postoji nepodudarnost između izgleda spoljašnjih polnih organa (fenotipski pol) i hromozomskog ili gonadnog pola (1,8,9). U nastanku ovih stanja značajnu ulogu imaju genetski i hormonski faktori, kao i faktori sredine tokom prenatalnog i postnatalnog razvoja (8). Poremećaji polne diferencijacije mogu klinički da se manifestuju na rođenju, u vidu ambivalentnog izgleda spoljašnjih genitalija ili tokom detinjstva i adolescentnog perioda u vidu poremećaja u razvoju sekundarnih polnih karakteristika. Prema podacima iz literature učestalost javljanja poremećaja polne diferencijacije iznosi približno 1: 4.500-5.500 (1,2,4,8,10,11).

Učestalost KAH-a i MGD-a kao najčešćih uzroka PPD-a se procenjuje na približno 1:15.000, odnosno 1:10.000 rođene dece (4). Učestalost sindroma potpune neosetljivosti na androgene, kao uzroka PPD-a, varira između 1:60.000 i 1:99.000, dok je sindrom parcijalne neosetljivosti na androgene češći (1). Daleko ređi uzroci PPD-a su deficit 17β-hidroksisteroid dehidrogenaze (17β-HSD), koji se javlja u 1:150.000 dece sa PPD-om, kao i deficit 5α-reduktaze (5α-RD), koji se javlja još ređe (1). U našem istraživanju učestalost GD-a iznosila je 54,8%, pri čemu je 23,5% ove dece imalo mešovitu formu GD, 41,2% imalo je parcijalnu formu, dok je preostalih 35,3% ove dece imalo druge forme GD. Sindrom neosetljivosti na androgene bio je zastupljen kod 9,7% dece sa PPD-om. Atipične forme KAH-a bile su uzrok PPD-a kod 6,5% dece, a kod 19,3% dece etiologija nije utvrđena.

Studija sprovedena 2006. godine u Nemačkoj ukazuje na pozitivnu porodičnu anamnezu u 6,3% ispitivanih pacijenata sa PPD-om (1). Rezultati našeg istraživanja, koji pokazuju pozitivnu porodičnu anamnezu kod 6,5% dece sa PPD-om, u skladu su sa ovakvim podacima.

U zavisnosti od kariotipa pacijenata sa poremećajem polne diferencijacije, ovi poremećaji se mogu svrstati u tri grupe: 46XY PPD, 46XX PPD i hromozomski PPD (12). Hromozomski PPD obuhvataju različite poremećaje kod kojih postoje strukturne ili numeričke anomalije polnih hromozoma, kao što su varijante Tarnerovog (45X monozomija ili 45X/46XY mozaicizam) i Klinefelterovog sindroma (47XXY). 46XY grupa PPD-a najčešće se manifestuje ambivalentnim izgledom spoljašnjih genitalija ili spoljašnjim genitalijama potpuno ženskog tipa usled smanjene ili odsutne maskulinizacije in utero. Uzrok ovog tipa PPD-a može da bude: 1) poremećen razvoj gonada što rezultuje parcijalnom ili kompletnom gonadnom disgenezijom, 2) defekt u biosintezi testosterona ili dihidrotestosterona, 3) odsustvo efekata androgena usled neosetljivosti ciljnih tkiva na androgene (sindrom potpune/parcijalne neosetljivosti na androgene – CAIS/PAIS) (11). 46XX gupa PPD-a najčešće se karakteriše ambivalentnim izgledom spoljašnjih genitalija usled ekspozicije fetusa prekomernom nivou androgena, uz normalan razvoj Milerovih struktura i ovarijuma. Prekomerna ekspozicija androgenima najčešće nastaje usled: 1) poremećaja u sintezi hormona nadbubrežne žlezde sa prekomernom produkcijom androgena (KAH), 2) deficita placentalne aromataze, 3) dejstva maternalnih androgenih hormona (ovarijalni ili adrenalni tumor, hormonska terapija) (12).

Rezultati istraživanja sprovedenog u Kolumbiji, kao i istraživanja sprovedenog od strane EU COST (engl. *European Cooperation in Science and Technology*), ukazuju na najveću učestalost kariotipa 46,XY među decom sa PPD-om (75%), a zatim kariotipa 46,XX (10-15%) i hromozomskog PPD-a (12,5%) (1,7,13,14). Ovakvi podaci u skladu su sa rezultatima našeg istraživanja, gde je među ispitivanom decom sa PPD-om kariotip 46,XY bio najzastupljeniji (77,42%), a potom hromozomski PPD (12,9%) i kariotip 46,XX (9,7%).

Prema istraživanju sprovedenom 2006. godine u Nemačkoj, oko polovina dece sa PPD-om nema postavljenu definitivnu dijagnozu do 6. meseca života (1,15). Prema rezultatima istog istraživanja, definitivna dijagnoza postavljena putem genetskih analiza utvrđena je kod 20% pacijenata sa PPD-om (15). U okviru našeg istraživanja utvrđeno je da je definitivna dijagnoza bez obzira na uzrast postavljena kod 25 pacijenata (81%). Dijagnoza je definitivno postavljena na osnovu: 1) hormonskih anali-

the presence of certain forms of gonadal dysgenesis (Table 4). Gonadal dysgenesis was the cause of DSD in 50% of children with 46XY DSD, 33% of children with 46XX DSD and in all children with chromosomal DSD, that is, with mixed gonadal dysgenesis (MGD). In 46XY group of DSD the most frequent (58.3%) was partial gonadal dysgenesis (PGD), whereas in 46XX group of DSD one child with gonadal dysgenesis (GD) had De la Chapelle syndrome. Genital surgery was performed in greater number of children with chromosomal DSD (in 75% of these children) and in children with 46XX DSD (66.7%), while fewer children with 46XY DSD were subjected to genital surgery (18.2%) ($p<0.05$). The characteristics of patients relating to physical, laboratory, ultrasound and MR findings, as well as their treatment, depending on the group of DSD, are shown in Table 4.

Discussion

Disorders of sex development (DSD), that is, differences of sex development encompass a range of congenital conditions with a difference between the appearance of the external genitalia (phenotypic sex) and chromosomal or gonadal sex (1,8,9). Genetic and hormonal factors have a significant role in the onset of these conditions, as well as environmental factors during the prenatal and postnatal development (8). Disorders of sex development may be clinically manifested at birth as ambiguous external genitalia or during childhood and adolescence as disorders of secondary sexual development. According to the literature data, the frequency of disorders of sex development is approximately 1: 4,500-5,500 (1,2,4,8,10,11).

The frequency of CAH and MGD as the most frequent causes of DSD is estimated to be approximately 1:15,000, that is, 1:10,000 of newborns (4). The frequency of complete androgen insensitivity syndrome, as a cause of DSD, varies between 1:60,000 and 1:99,000, while of partial androgen insensitivity syndrome is more frequent (1). Far less frequent cause of DSD is the deficiency of 17ß-hydroxysteroid dehydrogenase (17ß-HSD), which occurs in 1:150,000 of children with DSD, as well as the deficiency of 5α-reductase (5α-RD) that occurs even less frequently (1). In our study, the frequency of GD amounted to 54.8%, while 23.5% of these children had a mixed form of GD, 41.2% had a partial form, and the remaining 35.3% of these children had other forms of GD. Androgen insensitivity syndrome was present in 9.7% of children with DSD. Atypical forms of CAH were causes of DSD in 6.5% of children, while in 19.3% of children the etiology was not established.

A study conducted in Germany in 2006 pointed to the positive family anamnesis in 6.3% of examined patients with DSD (1). The results of our study, which pointed to the positive family anamnesis in 6.5% of children with DSD, were in accordance with such data.

Depending on the karyotype of patients with disorders of sex development, these disorders may be classified into three groups: 46XY DSD, 46XX DSD and chromosomal DSD (12). Chromosomal DSD encompass different disorders with structural or numerical anomalies of sexual chromosomes, such as the variants of Turner (45X monosomia or 45X/46XY mosaicism) and Klinefelter syndrome (47XXY). 46XY group of DSD is most commonly manifested as ambiguous external genitalia or external genitalia that are completely female due to the decreased or absent masculinization in utero. A cause of this type of DSD may be: 1) disrupted development of gonads resulting in partial or complete gonadal dysgenesis, 2) defect in the biosynthesis of testosterone or dihydrotestosterone, 3) the absence of androgen effects due to insensitivity of target tissues to androgens (complete/partial androgen insensitivity syndrome – CAIS/PAIS) (11). 46XX group of DSD is most frequently manifested as ambiguous appearance of external genitalia due to the exposure of fetus to the excess level of androgen, with the normal development of Müllerian structures and ovaries. Exposure to excess androgens is most frequently caused by: 1) disorders of the synthesis of hormones of adrenal glands with the excessive production of androgens (CAH), 2) placental aromatase deficiency, 3) the activity of maternal androgen hormones (ovarian and adrenal tumor, hormonal therapy) (12).

The results of one study conducted in Columbia, as well as the study conducted by EU COST (European Cooperation in Science and Technology), pointed to the highest frequency of karyotype 46XY among children with DSD (75%), and then karyotype 46XX (10-15%) and chromosomal DSD (12.5%) (1,7,13,14). These data are in accordance with the results of our study, where karyotype 46XY was the commonest among the examined-

Tabela 2. Anamnestički i dijagnostički podaci o pacijentima sa poremećajima polne diferencijacije (PPD)

Karakteristike	N=31 Broj (%) / $\bar{x}$± SD
Uzrast u trenutku javljanja lekaru zbog PPD	
Neonatalni uzrast	22 (71,0)
Detinjstvo	5 (16,1)
Adolescencija	4 (12,9)
Razlog prvog javljanja lekaru	
Ambivalentan izgled spoljašnjih genitalija	20 (64,5)
Nepodudarnost između nalaza prenatalnog/ postnatalnog kariotipa i izgleda polnih organa na rođenju	4 (12,9)
Virilizacija kod devojčica	1 (3,2)
Primarna amenoreja	1 (3,2)
Udruženo primarna amenoreja i virilizacija	2 (6,4)
Nizak rast	1 (3,2)
Ostalo	2 (6,4)
Grupa PPD	
46,XX PPD	3 (9,7)
46,XY PPD	24 (77,4)
Hromozomski PPD	4 (12,9)
Pozitivna porodična anamneza	2 (6,4)
Postavljena definitivna dijagnoza	25 (80,6)
Dijagnoza	
Gonadna disgenezija	17 (54,8)
Sindrom rezistencije na androgene	3 (9,7)
KAH (atipične forme)	2 (6,4)
Ostalo	3 (9,7)
Nije utvrđena etiologija	6 (19,4)
Tip gonadne disgenezije (GD) (% od uk. broja GD)	
Mešovita GD	4 (23,5)
Parcijalna GD	7 (41,2)
Ostale forme GD	6 (35,3)
Dijagnoza definitivno postavljena na osnovu	
Hormonskih nalaza	12 (48,0)
Genetskih analiza	8 (32,0)
Biopsije	2 (8,0)
Kliničkog ili radiološkog nalaza	3 (12,0)
Dijagnoza potvrđena hormonskim analizama	20 (64,5)
Prisustvo pridruženih malformacija	16 (51,6)
Pridružene malformacije (% od uk. broja malformacija)	
Urogenitalne	5 (31,2)
Malformacije CNS-a	1 (6,3)
Malformacije ekstremiteta	1 (6,3)
Nizak rast	4 (25,0)
Ostale malformacije	2 (12,5)
Udružene urogenitalne malformacije, malformacije CNS-a, ekstremiteta, srca, i nizak rast	1 (6,3)
Udružene malformacije CNS-a, srca i ostale malformacije	1 (6,3)
Udružene malformacije ekstremiteta, srca i ostale malormacije	1 (6,3)
Smrtni ishod pacijenta u prvih 12 meseci	2 (6,5)
Savetovano podizanje detata	
Muški pol	9 (29)
Ženski pol	5 (16,1)
Nije data preporuka	17 (54,8)
Izgled spoljašnjih genitalija – EGS	5,35±3,22
Gonade viđene na MR	5 (16,1)
Gonade viđene na UZ	19 (61,3)
Uterus viđen na MR	3 (50,0)
Uterus viđen na UZ	12 (40,0)

Table 2. Anamnestic and diagnostic data about patients with disorders of sex development (DSD) (1/2)

Characteristics	N=31 No (%) / $\bar{x}$ ± SD
Age at the time of first visit to a doctor due to DSD	
Neonatal period	22 (71.0)
Childhood	5 (16.1)
Adolescence	4 (12.9)
Reason for the first visit to a doctor	
Ambiguous external genitalia	20 (64.5)
Mismatch between prenatal/postnatal karyotype findings and genital appearance at the birth	4 (12.9)
Virilization of females	1 (3.2)
Primary amenorrhea	1 (3.2)
Primary amenorrhea and virilization	2 (6.4)
Low growth	1 (3.2)
Other reasons	2 (6.4)
DSD categories	
46,XX DSD	3 (9.7)
46,XY DSD	24 (77.4)
Chromosomal DSD	4 (12.9)
Positive family anamnesis	2 (6.4)
Definitive diagnosis	25 (80.6)
Diagnosis	
Gonadal dysgenesis	17 (54.8)
Androgen insensitivity syndrome	3 (9.7)
CAH (nonclassical types)	2 (6.4)
Other	3 (9.7)
Unknown etiology	6 (19.4)
Type of gonadal dysgenesis (GD) (% of total no. of GD)	
Mixed GD	4 (23.5)
Partial GD	7 (41.2)
Other forms GD	6 (35.3)
A definitive diagnosis was made by	
Hormonal analysis	12 (48.0)
Genetic analysis	8 (32.0)
Biopsy	2 (8.0)
Clinical and radiology findings	3 (12.0)
Diagnosis confirmed by hormonal analysis	20 (64.5)
Malformations associated with DSD	16 (51.6)
Types of malformations (% of total no. of malformations)	
Urogenital	5 (31.2)
CNS malformations	1 (6.3)
Extremities malformations	1 (6.3)
Low growth	4 (25.0)
Other malformations	2 (12.5)
United urogenital malformations. malformations of CNS. extremities. heart and low growth	1 (6.3)
United malformations of CNS. heart and other malformations	1 (6.3)
United malformations of extremities. heart and other malformations	1 (6.3)
Death of patients with DSD in first 12 months	2 (6.5)
Recommended gender of the child with DSD	9 (29.0)
Male	5 (16.1)
Female	17 (54.8)
No recommendation	
External genitalia score (EGS) ($\bar{x}$ ± SD)	5.35±3.22
Gonads visualized by MR	5 (16.1)
Gonads visualized by ultrasound	19 (61.3)
Uterus visualized by MR	3 (50.0)
Uterus visualized by ultrasound	12 (40.0)

Tabela 2. Anamnestički i dijagnostički podaci o pacijentima sa poremećajima polne diferencijacije (PPD) - nastavak (2/2)

Karakteristike	N=31 Broj (%) / $\bar{x}$ ± SD
Sindrom gubitka soli	0 (0,0)
Akutna adrenalna insuficijencija	0 (0,0)
Medikamentna endokrinološka terapija	10 (32,3)
Hidrokortizon	3 (9,7)
Fludrokortizon	1 (3,2)
Testosteron	0 (0,0)
E2	5 (16,1)
GnRH analog	3 (9,7)
Dete podizano u:	
muškom polu	18 (60,0)
ženskom polu	12 (40,0)
Genitalna hirurgija	9 (31,0)
Uzrast u trenutku prve genitalne hirurgije (god) ($\bar{x}$ ± SD)	5,29±3,99
Gonadektomija	7 (23,3)
Uzrast u trenutku gonadektomije (god) ($\bar{x}$ ± SD)	7,84 ±5,30
Biopsija gonada (podatak dostupan za 29 pacijenata)	9 (31,0)
Uzrast u trenutku poslednje kontrole (god) ($\bar{x}$ ± SD)	6,93 ± 6,59

$\bar{x}$ - aritmetička sredina, SD - standardna devijacija, PPD – poremećaji polne diferencijacije, KAH– kongenitalna adrenalna hiperplazija, GD – gonadalna disgenezija, UZ – ultrazvuk, MR – magnetna rezonanca, E2 – estradiol, GnRH – gonadotropin oslobađajući hormon, CNS–centralni nervni sistem, EGS–*External genitalia score*

za kod 48% dece, 2) genetskih analiza (uključujući nalaz kariotipa) kod 32% dece, 3) biopsije kod 8% dece, 4) kliničkih i radioloških nalaza kod 3% dece sa PPD-om. Defintivna dijagnoza kod većeg broja dece (89%) postavljena je u periodu 2 (2016-2020) u odnosu 69% u periodu 1 (2007-2015). U periodu 2 takođe je veći broj dijagnoza postavljen putem genetskih analiza (37,5%), nego u periodu 1 (22,2%).

Prema ranijim preporukama Akademije američkih pedijatara (engl. American Academy of Pediatrics) optimalnim uzrastom za izvođenje genitalne hirurgije (genitoplastike) kod dece sa PPD-om smatrao se uzrast između 2. i 6. meseca života (4,16). Međutim, prema novijim preporukama hirurški tretman pacijenata sa PPD preporučuje se u značajno kasnijem uzrastu deteta, idealno u cilju omogućavanja učestvovanja u donošenju odluke o hirurškoj intervenciji (4).

Rezultati našeg istraživanja su u skladu sa ovom izmenom smernica, gde je pokazana statistički značajna razlika ($p<0,05$) između perioda 1 (2007-2015) i perioda 2 (2016-2020) u pogledu genitalne hirurgije. Genitoplastika je znatno češće vršena kod dece u periodu 1 (64%) nego kod dece u periodu 2 (11%). Takođe, genitalna hirurgija tokom perioda 2 je bila u proseku u starijem uzrastu dece (6,8 ± 6,5) u odnosu na decu podvrgnutu genitalnoj hirurgiji u periodu 1 (4,8 ± 3,6).

U našem istraživanju kod 51,6% dece sa PPD-om utvrđeno je prisustvo pridruženih nalaza, najčešće se radilo o urogenitalnim malforacijama (31,2%), niskom rastu (25,0%), malformacijama centralnog nervnog sistema (6,3%) i ekstremiteta (6,3%). S obzirom na složenost dijagnostičkog i terapijskog pristupa poremećajima polne diferencijacije, u ispitivanju i lečenju ove dece neophodan je multidisciplinarni pristup tima stručnjaka koji sačinjavaju brojni specijalisti, a najčešće podrazumeva: pedijatra endokrinologa, neonatologa, dečjeg urologa, ginekologa, radiologa, psihijatra ili psihologa i socijalnog radnika (4,6,17).

Zaključak

Poremećaji polne diferencijacije obuhvataju etiološki heterogenu grupu stanja, koja zahteva holistički pristup radi što preciznijeg sagledavanja pacijenata i pružanja adekvatnog i individualizovanog tretmana i nege. U našem istraživanju dece sa PPD-om (uz isključivanje dece sa KAH-om usled deficita 21-hidroksilaze) najčešći uzroci PPD-a bili su: gonadna disgenezija, sindrom rezistencije na

Table 2. Anamnestic and diagnostic data about patients with disorders of sex development (DSD) (2/2)

Characteristics	N=31 No (%) / $\bar{x}$ ± SD
Salt wasting syndrome	0 (0.0)
Acute adrenal insufficiency	0 (0.0)
Hormonal therapy	10 (32.3)
Hydrocortisone	3 (9.7)
Fludrocortisone	1 (3.2)
Testosterone	0 (0.0)
E2	5 (16.1)
GnRH analogues	3 (9.7)
Child raised as	
Male	18 (60.0)
Female	12 (40.0)
Genital surgery	9 (31.0)
Age at the moment of first genital surgery ($\bar{x}$ ± SD)	5.29±3.99
Gonadectomy	7 (23.3)
Age at the moment of gonadectomy ($\bar{x}$ ± SD)	7.84 ±5.30
Gonadal biopsy (data available for 29 patients)	9 (31.0)
Age at the moment of last control ($\bar{x}$ ± SD)	6.93 ± 6.59

$\bar{x}$ – Mean, SD –Standard deviation, DSD – Disorders of sex development, GD – Gonadal dysgenesis, CAH- Congenital adrenal hyperplasia, MR – Magnetic resonance, E2 – estradiol, GnRH – Gonadotropin-releasing hormone, CNS – Central nervnous system, EGS-external genitalia score

children with DSD (77.42%), and then chromosomal DSD (12.9%) and karyotype 46XX (9.7%).

According to a study conducted in Germany in 2006, around one half of children with DSD did not have a definitive diagnosis until the sixth month of age (1,15). According to the results of the same study, a definitive diagnosis was made with the help of genetic analyses in 20% of patients with DSD (15). Within the scope of our study, it was found out that a definitive diagnosis was made in 25 patients regardless of patients' age (81%). The diagnosis was definitely made with the help of: 1) hormonal analyses in 48% of children, 2) genetic analyses (including the karyotype analysis) in 32% of children, 3) biopsy in 8% of children, 4) clinical and radiological findings in 3% of children with DSD. A definitive diagnosis was established in a larger number of children (89%) in the second period (2016-2020) in comparison to 69% in the first period (2007-2015). In the second period, more diagnoses were established with the help of genetic analyses (37.5%) than in the first period (22.2%).

According to the previous recommendations of the American Academy of Pediatrics, age between 2 and 6 months of life was deemed to be the optimal age for the introduction of genital surgery (genitoplasty) in children with DSD. However, according to recent recommendations, surgical treatment of patients with DSD is recommended at a significantly later age, aimed at enabling patients to make decisions about surgical interventions (4).

The results of our study are in accordance with these changes of guidelines, where statistically significant difference ($p<0.05$) between the period 1 (2007-2015) and period 2 (2016-2020) regarding genital surgery was shown. Genitoplasty was significantly more frequently performed in children in the first period (64%) than in the second period (11%). Also, during the second period genital surgery was performed at a later age (6.8 + 6.5) in comparison to children subjected to genital surgery in the first period (4.8 + 3.6).

In our study, in 51.6% of children with DSD, comorbid conditions were found, most commonly urogenital malformations (31.2%), short stature (25.0%), malformations of the central nervous system (6.3%) and extremities (6.3%). Considering the complexity of diagnostic and therapeutic approach to disorders of sex development, the examination and treatment of these children should necessarily involve a multidisciplinary approach of the team of specialists, including numerous specialists, most frequently pediatric endocrinologists, neonatologists, pediatric urologists, gynecologists, radiologists, psychiatrists or psychologists and social workers (4,6,17).

Tabela 3. Karakteristike ispitanika u zavisnosti od perioda ispitivanja u Institutu za zdravstvenu zaštitu majke i deteta Srbije - (1/2)

Karakteristike	Period 1 N= 13 Broj (%)	Period 2 N=18 Broj (%)	p vrednost
Uzrast u trenutku javljanja lekaru zbogPPD			
Neonatalni	9 (69,2)	13 (72,2)	> 0,05
Detinjstvo	3 (23,1)	2 (11,1)	
Adolescencija	1 (7,7)	3 (16,7)	
Razlog prvog javljanja lekaru			> 0,05
Ambivalentan izgled spoljašnjih genitalija	10 (76,9)	10 (55,6)	
Nepodudarnost između nalaza prenatalnog/postnatalnog kariotipa izgleda polnih organa na rođenju	1 (7,7)	3 (16,7)	
Virilizacija kod devojčica	0 (0,0)	3 (16,7)	
Primarna amenoreja	1 (7,7)	0 (0,0)	
Udruženo primarna amenoreja i virilizacija	0 (0,0)	2 (11,1)	
Nizak rast	1 (7,7)	0 (0,0)	
Ostalo	0 (0,0)	2 (11,1)	
Grupa PPD			
46,XX DSD	3 (23,1)	0 (0,0)	> 0,05
46,XY DSD	8 (61,5)	16 (88,9)	
Hromozomski DSD	2 (15,4)	2 (11,1)	
Pozitivna porodična anamneza	0 (0,0)	2 (11,1)	> 0,05
Postavljena definitivna dijagnoza	9 (69,2)	16 (88,9)	> 0,05
Dijagnoza			
Gonadna disgenezija	7(53,8)	10 (55,6)	> 0,05
Sindrom rezistencije na androgene	2 (15,4)	1 (5,6)	
KAH (atipične forme)	0 (0,0)	2 (11,1)	
Ostalo	0 (0,0)	3 (16,7)	
Nije utvrđena etiologija	4 (30,8)	2 (11,1)	
Izgled spoljašnjih genitalija-EGS ($\bar{x}$ ± SD)	4,7 ± 3,1	5,8 ± 3,3	> 0,05
Prisustvo pridruženih malformacija	5 (38,5)	11 (61,1)	> 0,05
Pridružene malformacije (% od uk. broja malformacija)			
Urogenitalne	1 (20,0)	4 (36,4)	> 0,05
Malformacije CNS-a	0 (0,0)	1 (9,1)	
Malformacije ekstremiteta	0 (0,0)	1 (9,1)	
Nizak rast	3 (60,0)	1 (9,1)	
Ostale malformacije	0 (0,0)	2 (18,2)	
Udružene urogenitalne malformacije, malformacije CNS-a, srca i ostale malformacije	0 (0,0)	1 (9,1)	
Udružene malformacije CNS-a, srca i ostale malformacije	1 (20,0)	0 (0,0)	
Udružene malformacije ekstremiteta, srca i ostale malformacije	1 (9,1)	0 (0,0)	
Smrtni ishod pacijenta u prvih 12 meseci	0 (0,0)	2 (11,1)	> 0,05
Gonadalna disgenezija tip (% od uk. broja GD)			
MGD	2 (28,6)	2 (20,0)	> 0,05
PGD	3 (42,9)	4 (40,0)	
Ostale forme GD	2 (28,6)	4 (40,0)	
Dijagnoza postavljena definitivno na osnovu			
Hormonskih nalaza	4 (44,4)	8 (50,0)	> 0,05
Genetskih analiza	2 (22,2)	6 (37,5)	
Biopsije	1 (11,1)	1 (6,3)	
Kliničkog i radiološkog nalaza	2 (22,2)	1 (6,3)	
Dijagnoza potvrđena hormonskim analizama	5 (38,5)	15 (83,3)	0,021
Dijagnoza potvrđena genetskim analizama	3 (23,1)	6 (33,3)	> 0,05
Gonade viđene na UZ	8 (61,5)	11 (61,1)	> 0,05
Gonade viđene na MR	1 (7,7)	4 (22,2)	> 0,05
Uterus viđen na UZ	6 (46,2)	6 (35,3)	> 0,05
Uterus viđen na MR	1 (50,0)	2 (50,0)	> 0,05
Sindrom gubitka soli	0 (0,0)	0 (0,0)	

Table 3. Characteristics of patients depending on the period of examination in the Mother and Child Health Care Institute of Serbia „Dr Vukan Cupic", Belgrade, Serbia (1/2)

Characteristics	Period 1 N= 13 No (%)	Period 2 N=18 No (%)	p value
Age at the time of first visit to a doctor due to DSD			
Neonatal period	9 (69.2)	13 (72.2)	> 0,05
Childhood	3 (23.1)	2 (11.1)	
Adolescence	1 (7.7)	3 (16.7)	
Reason for the first visit to a doctor			
Ambiguous external genitalia	10 (76.9)	10 (55.6)	> 0,05
Mismatch between prenatal/postnatal karyotype findings and genital appearance at the birth	1 (7.7)	3 (16.7)	
Virilization of females	0 (0.0)	3 (16.7)	
Primary amenorrhea	1 (7.7)	0 (0.0)	
Primary amenorrhea and virilization	0 (0.0)	2 (11.1)	
Low growth	1 (7.7)	0 (0.0)	
Other reasons	0 (0.0)	2 (11.1)	
DSD categories			
46.XX DSD	3 (23.1)	0 (0.0)	> 0,05
46.XY DSD	8 (61.5)	16 (88.9)	
Chromosomal DSD	2 (15.4)	2 (11.1)	
Positive family anamnesis	0 (0.0)	2 (11.1)	> 0.05
Definitive diagnosis	9 (69.2)	16 (88.9)	> 0.05
Diagnosis			
Gonadal dysgenesis	7(53.8)	10 (55.6)	> 0.05
Androgen insensitivity syndrome	2 (15.4)	1 (5.6)	
CAH (nonclassical types)	0 (0.0)	2 (11.1)	
Other	0 (0.0)	3 (16.7)	
Unknown etiology	4 (30.8)	2 (11.1)	
External genitalia score (EGS) $\bar{x} \pm SD$	4.7 ± 3.1	5.8 ± 3.3	> 0.05
Malformations associated with DSD	5 (38.5)	11 (61.1)	> 0.05
Types of malformations (% of total no. of malformations)			
Urogenital	1 (20.0)	4 (36.4)	> 0.05
CNS malformations	0 (0.0)	1 (9.1)	
Extremities malformations	0 (0.0)	1 (9.1)	
Low growth	3 (60.0)	1 (9.1)	
Other malformations	0 (0.0)	2 (18.2)	
United urogenital malformations. malformations of CNS. extremities. heart and low growth	0 (0.0)	1 (9.1)	
United malformations of CNS. heart and other malformations	1 (20.0)	0 (0.0)	
United malformations of extremities. heart and other malformations	1 (9.1)	0 (0.0)	
Death of patients with DSD in first 12 months	0 (0.0)	2 (11.1)	> 0.05
Type of gonadal dysgenesis (GD) (% of total no. of GD)			
Mixed GD	2 (28.6)	2 (20.0)	> 0.05
Partial GD	3 (42.9)	4 (40.0)	
Other forms GD	2 (28.6)	4 (40.0)	
A definitive diagnosis was made by			
Hormonal analysis	4 (44.4)	8 (50.0)	> 0.05
Genetic analysis	2 (22.2)	6 (37.5)	
Biopsy	1 (11.1)	1 (6.3)	
Clinical and radiology findings	2 (22.2)	1 (6.3)	
Diagnosis confirmed by hormonal analysis	5 (38.5)	15 (83.3)	0.021
Diagnosis confirmed by genetic analysis	3 (23.1)	6 (33.3)	> 0.05
Gonads visualized by MR	8 (61.5)	11 (61.1)	> 0.05
Gonads visualized by ultrasound	1 (7.7)	4 (22.2)	> 0.05
Uterus visualized by MR	6 (46.2)	6 (35.3)	> 0.05
Uterus visualized by ultrasound	1 (50.0)	2 (50.0)	> 0.05

Tabela 3. Karakteristike ispitanika u zavisnosti od perioda ispitivanja u Institutu za zdravstvenu zaštitu majke i deteta Srbije - nastavak (2/2)

Karakteristike	Period 1 N= 13 Broj (%)	Period 2 N=18 Broj (%)	p vrednost
Akutna adrenalna insuficijencija	13 (100,0)	18 (100,0)	
Medikamentna endokrinološka terapija	4 (30,8)	6 (33,3)	> 0,05
Hidrokortizon	0 (0,0)	3 (16,7)	> 0,05
Fludrokortizon	0 (0,0)	1 (5,6)	> 0,05
Testosteron	0 (0,0)	0 (0,0)	
E2	3 (23,1)	2 (11,1)	> 0,05
GnRH analog	0 (0,0)	3 (16,7)	> 0,05
Genitalna hirurgija	7 (63,6)	2 (11,1)	0,010*
Uzrast u trenutku prve genitalne hirurgije	4,8±3,6	6,83±6,46	> 0,05
Biopsija gonada	5 (45,5)	4 (22,2)	> 0,05
Gonandektomija	5 (41,7)	2 (11,1)	> 0,05
Uzrast u trenutku gonadektomije	7,2±6,3	9,3±2,6	> 0,05
Uzrast u trenutku poslednje kontrole	10,2±6,3	4,7±6,00	0,019*
Savetovano podizanje deteta			
Muški pol	5 (38,5)	4 (22,2)	> 0,05
Ženski pol	3 (23,1)	2 (11,1)	
Nije data preporuka	5 (38,5)	12 (66,7)	
Dete podizano u			
Muškom polu	6 (50,0)	12 (66,7)	> 0,05
Ženskom polu	6 (50,0)	6 (33,3)	

$\bar{x}$ – aritmetička sredina, SD– standardna devijacija, PPD – poremećaji polne diferencijacije, KAH–kongenitalna adrenalna hiperplazija, GD – gonadalna disgenezija, UZ – ultrazvuk, MR – magnetna rezonanca, E2 – estradiol, GnRH – gonadotropin oslobađajući hormon, CNS–centralni nervni sistem, EGS–*External genitalia score*, *p vrednost dobijena primenom Studentovog t testa

Table 3. Characteristics of patients depending on the period of examination in the Mother and Child Health Care Institute of Serbia „Dr Vukan Cupic", Belgrade, Serbia - continued (2/2)

Characteristics	Period 1 N= 13 No (%)	Period 2 N=18 No (%)	p value
Salt wasting syndrome	0 (0.0)	0 (0.0)	
Acute adrenal insufficiency	13 (100.0)	18 (100.0)	
Hormonal therapy	4 (30.8)	6 (33.3)	> 0.05
Hydrocortisone	0 (0.0)	3 (16.7)	> 0.05
Fludrocortisone	0 (0.0)	1 (5.6)	> 0.05
Testosterone	0 (0.0)	0 (0.0)	
E2	3 (23.1)	2 (11.1)	> 0.05
GnRH analogues	0 (0.0)	3 (16.7)	> 0.05
Genital surgery	7 (63.6)	2 (11.1)	0.010*
Age at the moment of first genital surgery	4.8±3.6	6.83±6.46	> 0.05
Gonadal biopsy	5 (45.5)	4 (22.2)	> 0.05
Gonadectomy	5 (41.7)	2 (11.1)	> 0.05
Age at the moment of gonadectomy	7.2±6.3	9.3±2.6	> 0.05
Age at the moment of last control	10.2±6.3	4.7±6.00	0.019*
Recommended gender of the child with DSD			
Male	5 (38.5)	4 (22.2)	> 0.05
Female	3 (23.1)	2 (11.1)	
No recommendation	5 (38.5)	12 (66.7)	
Child raised as			
Male	6 (50.0)	12 (66.7)	> 0.05
Female	6 (50.0)	6 (33.3)	

$\bar{x}$ – Mean, SD –Standard deviation, DSD – Disorders of sex development, GD – Gonadal dysgenesis, CAH- Congenital adrenal hyperplasia, MR – Magnetic resonance, E2 – estradiol, GnRH – Gonadotropin-releasing hormone, CNS – Central nervnous system, EGS-external genitalia score *p value obtained using Student's t test

Tabela 4. Karakteristike ispitanika u zavisnosti od grupe PPD - (1/2)

Karakteristike	46XX PPD N=3 Broj (%)	46XY PPD N=24 Broj (%)	Hromozomski PPD N=4 Broj (%)
Uzrast u trenutku prvog obraćanja lekaru zbog PPD			
Neonatalni/ odojački	2 (66,7)	18 (75,0)	2 (50,0)
Detinjstvo	1 (33,3)	3 (12,5)	1 (25,0)
Adolescencija	0 (0,0)	3 (12,5)	1 (25,0)
Razlog prvog javljanja lekaru zbog PPD			
Ambivalentan izgled spoljašnjih genitalija	2 (66,7)	15 (62,5)	3 (75,0)
Nepodudarnost između nalaza prenatalnog/ postanatalnog kariotipa i izgleda polnih organa na rođenju	1 (33,3)	3 (12,5)	0 (0,0)
Virilizacija kod devojčica	0 (0,0)	1 (4,2)	3 (12,5)
Primarnaamenoreja	0 (0,0)	2 (8,3)	0 (0,0)
Udruženo primarna amenoreja i virilizacija	0 (0,0)	1 (4,2)	0 (0,0)
Nizak rast	0 (0,0)	2 (8,3)	0 (0,0)
Ostalo	0 (0,0)	0 (0,0)	0 (0,0)
Pozitivna porodična anamneza	0 (0,0)	2 (8,3)	0 (0,0)
Postavljena definitivna dijagnoza	1 (33,3)	20 (83,3)	4 (100,0)
Dijagnoza			
Gonadna disgenezija	1 (33,3)	12 (50,0)	4 (100,0)
Sindrom rezistencije na androgene	0 (0,0)	3 (12,5)	0 (0,0)
KAH (atipične forme)	0 (0,0)	2 (8,0)	0 (0,0)
Ostalo	0 (0,0)	3 (12,5)	0 (0,0)
Nije utvrđena etiologija	2 (66,7)	4 (16,7)	0 (0,0)
Gonadalna disgenezija tip (% od uk. broja GD)			
MGD	0 (0,0)	0 (0,0)	4 (100,0)
PGD	0 (0,0)	7 (58,3)	0 (0,0)
Ostale forme	1 (100,0)	5 (41,7)	0 (0,0)
Dijagnoza postavljena defintivno na osnovu			
Hormonski nalazi	1 (100,0)	11 (55,0)	0 (0,0)
Genetske analize	0 (0,0)	4 (20,0)	0 (0,0)
Biopsija	0 (0,0)	2 (10,0)	0 (0,0)
Klinički i radiološki nalazi	0 (0,0)	3 (15,0)	0 (0,0)
Izgled spoljašnjih genitalija (EGS) ($\bar{x}$ ± SD)	6,5 ± 2,6	5,2 ± 3,5	5,5 ± 2,4
Dijagnoza potvrđena hormonskim analizama	0 (0,0)	17 (70,8)	3 (75,0)
Dijagnoza potvrđena genetskim analizama	1 (33,3)	4 (16,7)	4 (100,0)
Gonade viđene na UZ	2 (66,7)	14 (58,3)	3 (75,0)
Gonade viđene na MR	1 (100,0)	2 (100,0)	2 (100,0)
Uterus viđen na UZ	1 (33,3)	9 (39,1)	2 (50,0)
Uterus viđen na MR	1 (100,0)	0 (0,0)	0 (0,0)
Sindrom gubitka soli	0 (0,0)	0 (0,0)	0 (0,0)
Akutna adrenalna insuficijencija	0 (0,0)	0 (0,0)	0 (0,0)
Medikamentna endokrinološka terapija	0 (0,0)	7 (29,2)	3 (75,0)
Hidrokortizon	0 (0,0)	3 (12,5)	0 (0,0)
Fludrokortizon	0 (0,0)	1 (4,2)	0 (0,0)
Testosteron	0 (0,0)	0 (0,0)	0 (0,0)
E2	0 (0,0)	3 (12,5)	2 (50,0)
GnRH	0 (0,0)	2 (8,3)	1 (25,0)
Prisustvo pridruženih malformacija	1 (33,3)	12 (50,0)	3 (75,0)

Table 4. Characteristics of patients depending on DSD groups (1/2)

Characteristics	46XX DSD N=3 Number (%)	46XY DSD N=24 Number (%)	Chromosomal PPD N=4 Number (%)
Age at the time of first visit to a doctor due to DSD			
Neonatal period	2 (66.7)	18 (75.0)	2 (50.0)
Childhood	1 (33.3)	3 (12.5)	1 (25.0)
Adolescence	0 (0.0)	3 (12.5)	1 (25.0)
Reason for the first visit to a doctor			
Ambiguous external genitalia	2 (66.7)	15 (62.5)	3 (75.0)
Mismatch between prenatal/postnatal karyotype findings and genital appearance at the birth	1 (33.3)	3 (12.5)	0 (0.0)
Virilization of females	0 (0.0)	1 (4.2)	3 (12.5)
Primary amenorrhea	0 (0.0)	2 (8.3)	0 (0.0)
Primary amenorrhea and virilization	0 (0.0)	1 (4.2)	0 (0.0)
Low growth	0 (0.0)	2 (8.3)	0 (0.0)
Other reasons	0 (0.0)	0 (0.0)	0 (0.0)
Positive family anamnesis	0 (0.0)	2 (8.3)	0 (0.0)
Definitive diagnosis	1 (33.3)	20 (83.3)	4 (100.0)
Diagnosis			
Gonadal dysgenesis	1 (33.3)	12 (50.0)	4 (100.0)
Androgen insensitivity syndrome	0 (0.0)	3 (12.5)	0 (0.0)
CAH (nonclassical types)	0 (0.0)	2 (8.0)	0 (0.0)
Other	0 (0.0)	3 (12.5)	0 (0.0)
Unknown etiology	2 (66.7)	4 (16.7)	0 (0.0)
Type of gonadal dysgenesis (GD) (% of total no. of GD)			
Mixed GD	0 (0.0)	0 (0.0)	4 (100.0)
Partial GD	0 (0.0)	7 (58.3)	0 (0.0)
Other forms GD	1 (100.0)	5 (41.7)	0 (0.0)
Diagnosis confirmed by			
Hormonal analysis	1 (100.0)	11 (55.0)	0 (0.0)
Genetic analysis	0 (0.0)	4 (20.0)	0 (0.0)
Biopsy	0 (0.0)	2 (10.0)	0 (0.0)
Clinical and radiology findings	0 (0.0)	3 (15.0)	0 (0.0)
External genitalia score (EGS) ($\bar{x}$ ± SD)	6.5 ± 2.6	5.2 ± 3.5	5.5 ± 2.4
Diagnosis confirmed by hormonal analysis	0 (0.0)	17 (70.8)	3 (75.0)
Diagnosis confirmed by genetic analysis	1 (33.3)	4 (16.7)	4 (100.0)
Gonads visualized by MR	2 (66.7)	14 (58.3)	3 (75.0)
Gonads visualized by ultrasound	1 (100.0)	2 (100.0)	2 (100.0)
Uterus visualized by MR	1 (33.3)	9 (39.1)	2 (50.0)
Uterus visualized by ultrasound	1 (100.0)	0 (0.0)	0 (0.0)
Salt wasting syndrome	0 (0.0)	0 (0.0)	0 (0.0)
Acute adrenal insufficiency	0 (0.0)	0 (0.0)	0 (0.0)
Hormonaltherapy	0 (0.0)	7 (29.2)	3 (75.0)
Hydrocortisone	0 (0.0)	3 (12.5)	0 (0.0)
Fludrocortisone	0 (0.0)	1 (4.2)	0 (0.0)
Testosterone	0 (0.0)	0 (0.0)	0 (0.0)
E2	0 (0.0)	3 (12.5)	2 (50.0)
GnRH analogues	0 (0.0)	2 (8.3)	1 (25.0)
Malformations associated with DSD	1 (33.3)	12 (50.0)	3 (75.0)
Child raised as			
Male	1 (33.3)	15 (65.2)	2 (50.0)
Female	2 (66.7)	8 (34.8)	2 (50.0)
Genital surgery	2 (66.7)	4 (18.2)	3 (75.0)

Tabela 4. Karakteristike ispitanika u zavisnosti od grupe PPD nastavak - nastavak (2/2)

Karakteristike	46XX PPD N=3 Broj (%)	46XY PPD N=24 Broj (%)	Hromozomski PPD N=4 Broj (%)
Pridružene malformacije (% od uk. broja malformacija)			
Urogenitalne	1 (100,0)	4 (33,2)	0 (0,0)
Malformacije CNS-a	0 (0,0)	1 (8,3)	0 (0,0)
Malformacije ekstremiteta	0 (0,0)	1 (8,3)	0 (0,0)
Nizak rast	0 (0,0)	1 (8,3)	3 (100,0)
Ostale malformacije	0 (0,0)	2 (16,6)	0 (0,0)
Udružene urogenitalne malformacije, malformacije CNS-a, srca i ostale malformacije	0 (0,0)	1 (8,3)	0 (0,0)
Udružene malformacije CNS-a, srca i ostale malformacije	0 (0,0)	1 (8,3)	0 (0,0)
Udružene malformacije ekstremiteta, srca i ostale malormacije	0 (0,0)	1 (8,3)	0 (0,0)
Smrtni ishod pacijenta u prvih 12 meseci	0 (0,0)	2 (8,3)	0 (0,0)
Savetovano podizanje deteta			
Muški pol	1 (33,3)	7 (29,2)	1 (25,0)
Ženski pol	1 (33,3)	3 (12,5)	1 (25,0)
Nije data preporuka	1 (33,3)	14 (58,3)	2 (50,0)
Dete podizano u			
Muškom polu	1 (33,3)	15 (65,2)	2 (50,0)
Ženskom polu	2 (66,7)	8 (34,8)	2 (50,0)
Genitalna hirurgija	2 (66,7)	4 (18,2)	3 (75,0)
Uzrast u trenutku prve genitalne hirurgije (godine) ($\bar{x}$ ± SD)	7.90±5.35	2.48±1.16	7.28±4.33
Gonadektomija	0 (0,0)	4 (17,4)	3 (75,0)
Uzrast u trenutku gonadektomije (godine) ($\bar{x}$ ± SD)		8.33±5.48	7.17± 6.17
Biopsija gonada	0 (0,0)	6 (27,3)	3 (75,0)
Uzrast u trenutku poslednje kontrole ($\bar{x}$ ± SD)	8.95±10.50	6.20±6.36	9.65±5.64

$\bar{x}$ - aritmetička sredina, SD-standardna devijacija , PPD – poremećaji polne diferencijacije, GD – gonadalna disgenezija, UZ – ultrazvuk, MR – magnetna rezonanca, E2 – estradiol, GnRH – gonadotropin oslobađajući hormon, CNS-centralni nervni sistem, EGS– *External genitalia score*.

androgene i atipične forme KAH. Utvrđeno je da je u drugom periodu (2016-2020) zbog PPD-a ispitivan veći broj dece sa PPD-om u IMD-u, kao i da se povećao procenat PPD-a sa utvrđenom etiologijom u odnosu na prvi period (2007-2015). Takođe, naši podaci ukazuju da se dijagnoza sve češće postavlja na osnovu genetskih analiza, a da se genitoplastika sprovodi kod sve manjeg broja dece i u kasnijem uzrastu.

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Table 4. Characteristics of patients depending on DSD groups - continued (2/2)

Characteristics	46XX DSD N=3 Number (%)	46XY DSD N=24 Number (%)	Chromosomal PPD N=4 Number (%)
Types of malformations (% of total no. of malformations)			
Urogenital	1 (100.0)	4 (33.2)	0 (0.0)
CNS malformations	0 (0.0)	1 (8.3)	0 (0.0)
Extremities malformations	0 (0.0)	1 (8.3)	0 (0.0)
Low growth	0 (0.0)	1 (8.3)	3 (100.0)
Other malformations	0 (0.0)	2 (16.6)	0 (0.0)
United urogenital malformations. malformations of CNS. extremities. heart and low growth	0 (0.0)	1 (8.3)	0 (0.0)
United malformations of CNS. heart and other malformations	0 (0.0)	1 (8.3)	
United malformations of extremities. heart and other malformations	0 (0.0)	1 (8.3)	0 (0.0) 0 (0.0)
Death of patients with DSD in first 12 months	0 (0.0)	2 (8.3)	0 (0.0)
Recommended gender of the child with DSD			
Male	1 (33.3)	7 (29.2)	1 (25.0)
Female	1 (33.3)	3 (12.5)	1 (25.0)
No recommendation	1 (33.3)	14 (58.3)	2 (50.0)
Age at the moment of first genital surgery ($\bar{x}$ ± SD)	7.90±5.35	2.48±1.16	7.28±4.33
Gonadectomy	0 (0.0)	4 (17.4)	3 (75.0)
Age at the moment of gonadectomy		8.33±5.48	7.17± 6.17
Gonadal biopsy	0 (0.0)	6 (27.3)	3 (75.0)
Age at the moment of last control ($\bar{x}$ ± SD)	8.95±10.50	6.20±6.36	9.65±5.64

$\bar{x}$ – Mean, SD –Standard deviation, DSD – Disorders of sex development, GD – Gonadal dysgenesis, MR – Magnetic resonance, E2 – estradiol, CAH- Congenital adrenal hyperplasia, GnRH – Gonadotropin-releasing hormone, CNS – Central nervnous system, EGS-external genitalia score.

Conclusion

Disorders of sex development encompass a heterogeneous group of conditions with different etiology, which demand a holistic approach in order to evaluate patients more precisely and provide appropriate and individualized treatment and care. In our study that included children with DSD (with the exclusion of children with CAH due to 21-hydroxylase), the most frequent reasons for DSD were the following: gonadal dysgenesis, androgen insensitivity syndrome and atypical forms of CAH. It was found out that in the second period (2016-2020) a larger number of children with DSD were examined at Mother and Child Health Care Institute, as well as that the percentage of DSD with the established etiology increased in comparison to the first period (2007-2015). Also, our data pointed to the fact that the diagnosis was more frequently established with the help of genetic methods, and that genitoplasty was performed in fewer children and at a later age.

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Autor za korespondenciju: klinički asistent, dr Rade Vuković, Medicinski fakultet Univerziteta u Beogradu, Institut za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Cupic", Radoja Dakića 8, 11070 Beograd, Srbija; e-mail: radevukovic9@gmail.com

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Corresponding author: clinical assistant, Rade Vukovic, MD, School of Medicine, University of Belgrade, Mother and Child Health Care Institute of Serbia „Dr Vukan Cupic", Radoja Dakica 8, 11070 Belgrade, Serbia; e-mail: radevukovic9@gmail.com