MARIANA SPRINCEAN[1,2], SVETLANA HADJIU[1,2], ELENA HALABUDENCO[2], LILIANA FUIOR[1,2], STELA RACOVITSA[1], V. EGOROV[1,2], NATALIA BARBOVA[1,2], B.M.L. NEAMTSU[3], M.L. NEAMTSU[3], CORNELIA CALCII[1,2], NINEL REVENCO[1,2]

ROLE OF MEDICO-GENETIC COUNSELING AND PRENATAL SCREENING IN DIAGNOSIS OF RENAL URINARY PATHOLOGY IN FETUS

[1] State Medical and Pharmaceutical Unversity "Nicolae Testemitsanu", Chisinau, Republic of Moldova
[2] Institute Mother and Child, Chisinau, Republic of Moldova
[3] Sibiu University, Department of Medicine, Romania

SUMMARY

Key words: medical-genetic counseling, renal urinary pathology, screening, fetus.
Introduction. Prenatal diagnosis of fetal kidney disease (FKD) is a very important field of contemporary medicine, and especially of medical genetics and nephrology. The purpose of this study is to highlight the role of the medical-genetic counseling and prenatal screening in the diagnosis of fetal renal urinary pathology. *Materials and methods.* In the process of the investigation the medical-genetic counseling was used, which aimed to identify the target group, i. e., 573 pregnant women suspected for fetal congenital anomalies including fetal renal urinary diseases, examined in the Institute of Mother and Child, in 2016 – 2019. *Methods:* medico-genetic counseling and prenatal ultrasound screening. *Results.* Clinical-genetic examination and interpretation of paraclinical and ultrasonographic findings allowed the diagnosis of FKD in fetuses in 76 cases. The data obtained indicate that the most frequent FKD diagnosed was renal multicystosis – 14 cases (18.4±4.45%), followed by renal agenesis 11 cases (14.5±4.04%). Among other renal anomalies, the most common were multiple anomalies (MA) associated with renal abnormalities – 10 cases (13.2±3.88%), renal polycystosis – 8 cases (10.5±3.52%), renal hypoplasia associated with oligohydramnios – 4 cases (5.2±2.56%), Potter syndrome – 3 cases (3.9±2.23%), and other FKD – 26 cases (34.2±5.44%), including megacystis, unilateral kidney aplasia, bilateral hydronephrosis, Prune Belly syndrome, etc. In 35 of the cases, pregnancy was interrupted following medical indications. During the medical-genetic counseling, the geneticist, according to the understanding of proband, informed about the degree of risk, the complications and the possibilities of treatment of the child with FKD. The final decision to keep or discontinue the pregnancy rested with the couple, parents and / or future mother. *Conclusions.* Medico-genetic counseling and prenatal ultrasound screening are the most effective diagnostic methods of FKD in fetuses. The methods of prenatal diagnosis, starting with the earliest ontogenetic periods, allow the early detection of FKD, as well as avoiding the birth of children with severe renal urinary pathologies. This method is indicated to prevent the birth of children with FKD.

РЕЗЮМЕ

РОЛЬ МЕДИКО-ГЕНЕТИЧЕСКОЙ КОНСУЛЬТАЦИИ И ПРЕНАТАЛЬНОГО СКРИНИНГА В ДИАГНОСТИКЕ ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ МОЧЕВЫДЕЛИТЕЛЬНОЙ СИСТЕМЫ У ПЛОДА

Ключевые слова: медико-генетическое консультирование, врожденные пороки, мочевыделительная система, скрининг, плод.
Введение. Пренатальная диагностика врождённых пороков развития мочевыделительной системы (ВПРМС) у плода является довольно важным разделом современной медицины, особенно медицинской генетики и нефрологии. *Целью* данной работы является освещение роли медико-генетической консультации и пренатального скрининга в диагностике врождённых пороков развития мочевыделительной системы у плода. *Материалы и методы.* В процессе исследования использовалась медико-генетическая консультация, целью которой было выявить целевую группу – 573 беременных, подозреваемых на врождённые пороки развития плода, в том числе мочевыделительной системы, отправленных на обследование в Институт Матери и Ребенка в 2016-2019 гг. Методы состояли в применении медико-генетического консультировании и пренатального ультразвукового скрининга. *Результаты.* Клинико-генетическое исследование и интерпретация параклинических и ультразвуковых данных позволили поставить диагноз ВПРМС у плода в 76 случаях. Полученные данные показыва-

ют, что наиболее частым диагнозом ВПРМС у плода был почечный мультикистоз – 14 случаев (18,4±4,45%), агенезия почек – 11 случаев (14,5±4,04%). Среди других пороков развития почек наиболее распространены: множественные аномалия развития при наличии аномалий почек – 10 случаев (13,2±3,88%), поликистоз почек – 8 случаев (10,5±3,52%), гипоплазия почек, связанная с маловодием – 4 случая (5,2±2,56%), синдром Поттера – 3 случая (3,9±2,23%) и другие ВПРМС – 26 случаев (34,2±5,44%), в том числе гигантская киста, односторонняя аплазия почки, двухсторонний гидронефроз, синдром Prune Belly и др. В 35 случаях беременность была прервана по медицинским показаниям. Во время медико-генетического консультирования врач-генетик, в соответствии с пониманием пробанда, информировал его о степени риска, осложнениях и возможностях лечения ребенка с ВПРМС. Окончательное решение о сохранении или прерывании беременности принимается парой, родителями и / или будущей матерью. *Выводы.* Медико-генетическая консультация и пренатальный ультразвуковой скрининг являются наиболее эффективными методами диагностики ВПРМС у плода. Проведение пренатальной диагностики, начиная с самых ранних онтогенетических периодов, позволяет заблаговременно обнаружить ВПРМС, а также избежать рождения детей с тяжёлой патологией мочевыделительной системы. Этот метод показан для предотвращения рождения детей с ВПРМС.

REZUMAT

ROLUL CONSULTULUI MEDICO-GENETIC ȘI AL SCREENINGULUI PRENATAL ÎN DIAGNOSTICUL PATOLOGIILOR RENOURINARE LA FĂT

Cuvinte cheie: consult medico-genetic, patologie renourinară, screening, făt.
Introducere. Diagnosticul prenatal al patologiilor renourinare (PRU) la făt reprezintă un compartiment destul de important al medicinei contemporane, și în special al geneticii medicale și nefrologiei. *Scopul* lucrării de faţă constă în evidenţierea rolului consultului medico-genetic și al screeningului prenatal în diagnosticul patologiei renourinare la făt. *Material și metode.* În procesul investigaţiei s-a recurs la consultul medico-genetic, care a avut drept scop identificarea grupului-ţintă – 573 de gravide cu suspecţie pentru malformaţii congenitale fetale, inclusiv patologii renourinare la făt, trimise spre examinare la Institutul Mamei și Copilului, în perioada 2016-2019. Metode: consultul medico-genetic și screeningul ecografic prenatal. *Rezultate.* Examinarea clinico-genetică și interpretarea rezultatelor paraclinice și ultrasonografice au permis diagnosticarea PRU la fetuși în 76 de cazuri. Datele obținute denotă că cea mai frecventă PRU diagnosticată a fost multicistoza renală – 14 cazuri (18,4±4,45%), urmată de agenezia renală – 11 de cazuri (14,5±4,04%). Dintre alte patologii malformative renale, cele mai frecvente au fost: MCM, asociate cu anomalii renale – 10 cazuri (13,2±3,88%), polichistoza renală – 8 cazuri (10,5±3,52%), hipoplazia renală asociată cu oligoamnios – 4 cazuri (5,2±2,56%), sindromul Potter – 3 cazuri (3,9±2,23%), și alte PRU – 26 de cazuri (34,2±5,44%), inclusiv: megacistis, aplazia unilaterală a rinichiului, hidronefroză bilaterală, sindromul Prune Belly etc. În 35 din cazuri s-a recurs la întreruperea sarcinii după indicații medicale. În cadrul consilierii, medicul genetician a informat, pe înțelesul probandului, despre gradul de risc, complicațiile și posibilitățile de tratament al copilului cu PRU. Decizia finală de a păstra sau a întrerupe sarcina a revenit cuplului, părinților și/sau viitoarei mame. *Concluzii.* Consultul medico-genetic și screeningul ecografic prenatal reprezintă cele mai eficiente metode de diagnostic al PRU la fetuși. Efectuarea unui diagnostic prenatal, începând cu perioade ontogenetice precoce, permite depistatea timpurie a PRU, prevenirea nașterii copiilor cu patologii renourinare severe.

Introduction.
Prenatal diagnosis of fetal renal urinary pathologies (RUP) represents a very important compartment of modern medicine, and especially of medical genetics and nephrology. Currently in the Republic of Moldova there are a large number of children with RUP, and their incidence remains constant over the last decades [8]. In recent decades in the Republic of Moldova the rate of congenital anomalies remains consistently high, ranking second in the structure of infant mortality, i., e.,: in 2009 – 27%, in 2010 – 29,4%, in 2011 – 27,1% and in 2012 – 36,4% [8]. In 2016-2019 in the structure of congenital anomalies in the Republic of Moldova was dominated by cardiovascular anomalies, i. e., 26%, followed by anomalies of the osteomuscular system (19%), multiple anomalies (18%), and anomalies of the urinary system (12%). In the same period, there was also a trend to increase the incidence of renal system anomalies – from 4,5% in 2011 to 9,4% in 2012 and up to 12,43% in 2019.
To date prenatally diagnosed renal urinary congenital anomalies (PDRU) are still not enough researched, especially in the Republic of Moldova. Prophylaxis of renal urinary congenital anomalies (RUCA) during pregnancy is performed at the population level using non-invasive and invasive prenatal diagnostic technologies (PD) [1]. PD can resolve a large volume of important problems and critical aspects related to the prophylaxis of fetal pathologies and the prevention of the birth of children with various pathologies

and pathological conditions including congenital anomalies of the renal urinary system [7]. Among the most commonly invasive PD methods amniocentesis is used to study of fetal cariotype at 16 – 18 weeks of pregnancy. Fetal ultrasound and biochemical screening, i. e., double and triple test are among of more widely used and informative methods of non-invasive PD for diagnosing ultrasound markers of some fetal RUCA. These methods of PD are considered to be safe and widely applied tests, and geneticist during the medical-genetic counseling conducts comprehensive and accurate information of the proband keeping in mind his fully understanding about the role, advantages, degree of risk, indications and contraindications of these investigations [2].

An important role in this process of information and promotion of effective methods of prophylaxis and working with the population plays the geneticist, in the framework of the genetic counseling. The medical-genetic counseling is the main point in the comprehensive medical service for pregnant women aiming to prophylaxis of hereditary diseases and fetal anomalies, including fetal RUCA [1, 4]. The essence of the medical-genetic counseling is in determining the prognosis of the birth of a child with hereditary and congenital pathologies, explaining the possibility of an unfavorable development of pregnancy and, in case of confirmation of a pathological pregnancy, in the aid of the woman or family to make a decision regarding the birth of the child [5, 11]. A difficult and crucial task in the process of antenatal verification of the fetal RUCA is the selection of a group of "fatal abnormalities" that require discussion about the need to terminate pregnancy or articulate the need to terminate the pregnancy on a medical indications [10].

The interest of pediatric geneticists and urologists in studying the antenatal period of the development of urinary system anomalies has contributed significantly to the increase in the quality of prenatal diagnosis of these conditions [6, 12]. Prenatal diagnosis of malformations of the fetal urinary system certainly requires the participation of a pediatric urologist in diagnosis and decisions about tactics, as well as the development of a system of organizing measures to ensure the introduction and practical use of the system of prenatal counseling [3].

The aim of this study is to highlight the role of medical-genetic counseling and prenatal screening in the diagnosis of fetal renal urinary pathology.

Materials and methods.

In the investigation process, the medical-genetic counseling was used, which aimed to identify the target group – 573 pregnant women with suspected fetal anomales, including fetal renal urinary pathology, addressed for investigation to the Institute of Mother and Child, between 2016 and 2019.

Results and discussions.

Clinical-genetic investigation and interpretation of paraclinical and ultrasonographic results allowed the diagnosis of RUCA in fetuses in 76 cases. The data obtained show that the most common RUCA diagnosed was renal multicystosis in 14 cases (18,4±4,45%), followed by renal agenesis in 11 cases (14,5±4,04%). Of the other renal malformative pathologies, the most common were multiple congenital anomalies associated with renal malformations in 10 cases (13,2±3,88%), polycistic kidney disease in 8 cases (10,5±3,52%), renal hypoplasia associated with oligohydramnios in 4 cases (5,2±2,56%), Potter syndrome in 3 cases (3,9±2,23%), and other RUCA in 26 cases (34,2±5,44%), including: megacystis, unilateral kidney aplasia, bilateral hydronephrosis, prune belly syndrome, etc. In 35 cases, termination of pregnancy was used for medical reasons. During the meical-genetic counseling the geneticist in the medical-genetic counseling conducts comprehensive and accurate information of the proband keeping in mind his fully understanding about the risk, complications and possibilities of treatment of RUCA in children. The final decision about the pregnancy can be taken by the couple, parents and/or future mother.

Common fetal anomalies of the kidneys and urinary tract comprise a complex spectrum of abnormalities that can be detected prenatally by ultrasound. These anomalies can affect the production of amniotic fluid which can

Table 1. Fetal renal urinary pathologies which are diagnosed using prenatal USG (number of the cases)

Fetal renal and urinary pathology	2016	2017	2018	2019	Total (cases)
Multycystic kidneys	4	3	3	4	14
Renal agenesis	3	3	2	3	11
MA associated with renal anomalies	3	2	2	3	10
Polycystic kidney disease	2	2	2	2	8
Renal hypoplasia associated with oligohydramnios	2	1	-	1	4
Potter sindrome	1	-	1	1	3
Others fetal RUCA	7	6	6	7	26
Total (cases)	22	17	16	21	76

lead to oligohydramnios or anhydramnios, resulting to fetal pulmonary hypoplasia and possibly abnormal development of other fetal structures.

The development of the fetal urinary tract is a complex process and is therefore associated with a substantial inevitable risk of congenital anomalies. Fetal anomalies of renal system makeup to 20% of all fetal congenital anomalies and are revealed in 3 – 4% of all pregnancies.

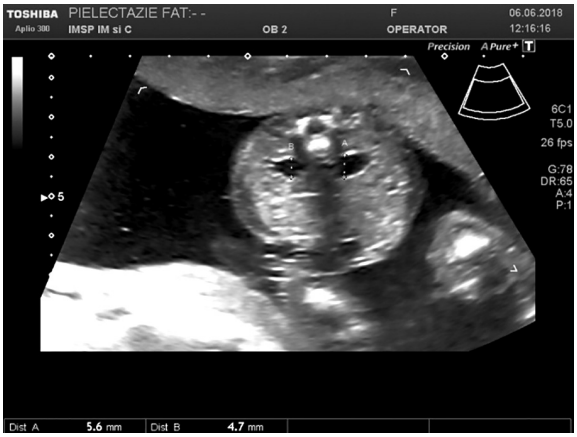


Fig. 1. Pyelectasis in the fetus.

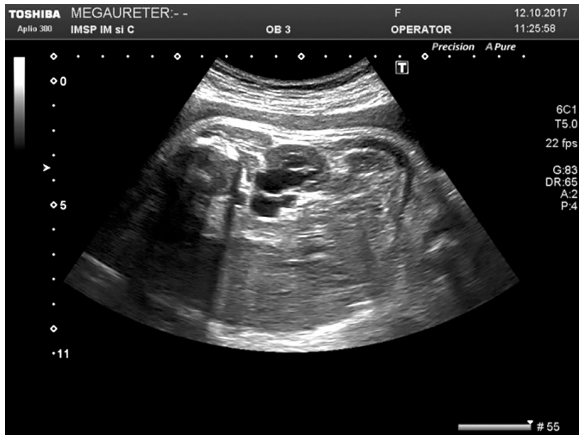


Fig. 2. Megaureter.

The frequency of common anomalies of renal and urinary system in the fetus which are detected prenatally observed with frequency of 0,1 – 2,3% [1, 2]. Urine produced by the fetal kidneys is a major contributor to the volume of amniotic fluid in the second and third trimester of pregnancy. Therefore, any structural or functional defects of the fetal urinary tract can lead to a substantial reduction in the volume of amniotic fluid, i. e., oligohydramnios or anhydramnios, which in turn can cause fetal pulmonary hypoplasia, as well as the abnormal development of several other fetal structures [3]. Fetal oligohydramnios or anhydramnios is associated with a severe outcome, with a reported mortality rate of 30 – 60% [4]. Precise diagnosis of common fetal anomalies of the kidneys and urinary tract is essential for parental counseling, proper pregnancy management and appropriate birth planning with a multidisciplinary team.

Anomalies of urinary system occupy one of the leading places in the structure of chronic kidney disease and causes of disability in children with congenital malformations. The relevance of the problem studied is determined by the progressive increase in the number of diseases, which are related etiologically and pathogenetically to the pathology of antenatal development.

Fetal pyelectasis usually consists of a slight enlargement of the central area of the kidney. Enlarging may be the result of the obstruction of urinary tract on the way from the kidneys to the bladder, especially in place of junction of renal pelvis and ureter. This causes extension of renal pelvis by urine pressure. Reflux of urine is also possible, i. e., return of urine from the bladder to the kidneys. Fetal pyelectasis requires follow-up, but not always need for treatment. Often the finding disappears spontaneously and has no negative impact on the fetus. As the increase in size is the result of pressure caused by obstruction of urine flow, surgery to correct the obstruction is often necessary after birth.

Below we will also present some cases of renal and urinary pathology diagnosed prenatally using the ultrasonography at the Institute of Mother and Child.

Megaureter or the dilated ureter is an anomaly of one or both ureters of a fetus. A megaureter is an extended or enlarged ureter that does not function normally. The diameter of a megaureter is usually more than 10 millimeters. Postnatal complications associated with the megaureter include reflux of urine into the kidneys and accumulation of urine inside the obstructed ureter. As a complication the pathology can cause a urinary tract infection. In some children megaureter can eventually lead to renal insufficiency.

Ultrasonographic markers of fetal RUCA are well described in the literature. Cystic dysplasia can be diagnosed in the presence of multiple cysts in the projection of the kidneys, observing of modified and enlarged kidneys. In the cases of unilateral kidney pathology, e. g., multicystic changes and renal aplasia, the absence of oligohydramnios is the factors that confirm the preservation of the functional state of a single kidney which have a favorable prognosis for the fetus and subsequently for the child.

One of the most serious congenital anomalies of the urinary system is bilateral renal agenesis. This abnormality can be isolated, but may also be observed in combination with other fetal syndromes and genetic abnormalities, including cardiovascular (15%) and musculoskeletal anomalies (40%), e. g., feet deformations. Less common associations include diaphragmatic hernia, tracheoesophageal fistula, hydrocephalus, myelomeningocele and duodenal atresia. The occurrence of renal agenesis with other abnormalities has been described as the association VACTERL, which refers to the association of vertebral abnormalities, anal atresia, heart defects, tracheoesophageal fistula or esophageal atresia, renal and radial anomalies and limb defects [10,

11]. Fetuses with bilateral renal agenesis present the Potter phenotypic sequence, which is characterized by retroposition of mandibular, a receding chin, low-set ears, wide-distance eyes with epicant folds and a wide nasal bridge. These facial features are due to a lack of amniotic fluid, which, in normal development, protects the fetus' face from injuries to the uterine walls [12]. The absence of both kidneys and renal arteries can be detected in the paravertebral regions using ultrasound (Fig. 2). In the process of growing in an empty renal fossa, the adrenal glands stretch longitudinally, taking an elongated shape, i. e., "the lying position". In some cases, the elongated adrenal glands can take an ovoid form, simulating the appearance of the kidneys. Severe oligohydramnios is usually observed in the establishment of bilateral renal agenesis. Oligohydramnios tends to be more evident after 16 weeks of gestation, since the initial production of urine by the placenta gradually decreases until then, without the viable kidneys being able to perform this function.

With the development of ultrasound diagnosis and monitoring of the fetus in the early stages of pregnancy, it is possible to identify congenital pathology of the urinary system even in utero. Antenatal urology, as combining of prenatal diagnosis and pediatric urology, gave a powerful incentive to the study of the development of urinary system anomalies in the antenatal period, which allows determining the prognosis of the revealed pathological condition. This will be a real measure to reduce the number of severe defects using prevention, prenatal correction, informed and early treatment in the postnatal period or the termination of fatal conditions incompatible with life.

The informative periods of ultrasonographic visualization of fetal RUCA are ultrasound at 11 ÷ 13 + 6, 18 ÷ 21 and 30 ÷ 34 weeks of gestation. Subsequently, screening of a pregnant woman is used, to address the problem of prenatal counseling and participation of a team of a neonatologist (urologist) surgeon, and determining the tactics of pregnancy and childbirth.

Cases of fetal megacystis were diagnosed during the informative periods of fetal visualization. Approximately 50% of pregnancies with megacystis ceased, but this proportion varied taking into account important factors such as oligohydramnios, gestational age, degree of bladder enlargement, hyperecogenic kidneys, cariotype and gender.

Clinical congenital anomalies of the fetus can be divided into: a) favorable, i. e., anomalies which are compatible with life after birth and not requiring serious surgical treatment; (b) conditionally unfavorable, i. e., with a real possibility of normal development of the child after appropriate surgical or other assistance, and c) unfavorable with serious defects, incompatible with life after birth under any conditions or leading to severe disability of the child.

Hyperecogenic kidneys is a serious problem faced by geneticists, obstetricians and urologists in the counseling of pregnant women following the ultrasound prenatal diagnosis of fetal abnormalities with an uncertain prognosis. This underlines the need to base prenatal counseling on prenatal cohorts with long-term postnatal follow-up. Firstly, fetal ultrasound usually fails to provide an accurate explanation of etiological causes, and the diagnosis of fetal hyperecogenic kidneys can result from a variety of causes. Secondly, within each etiological group, there is a wide range of postnatal outcomes, from more

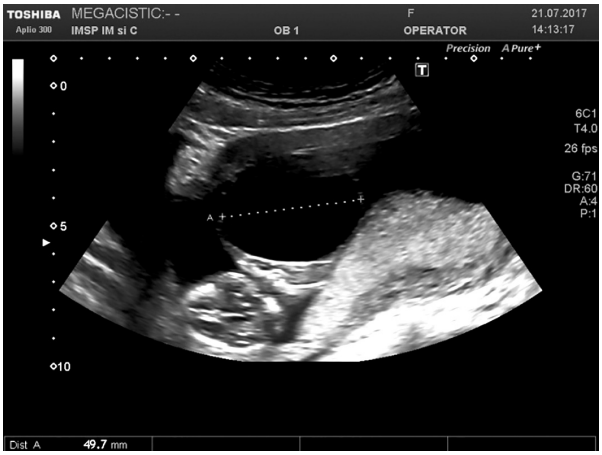
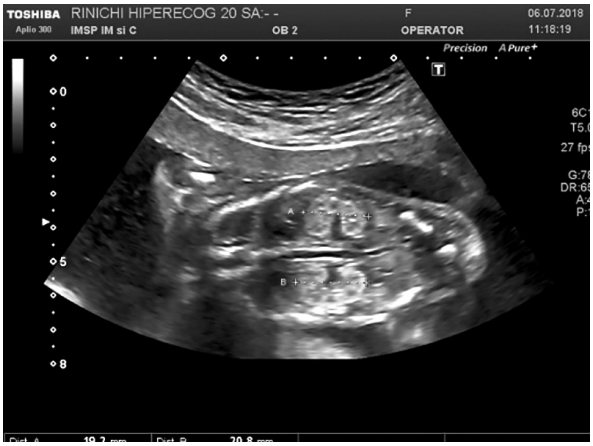


Fig. 3. Megacystis.



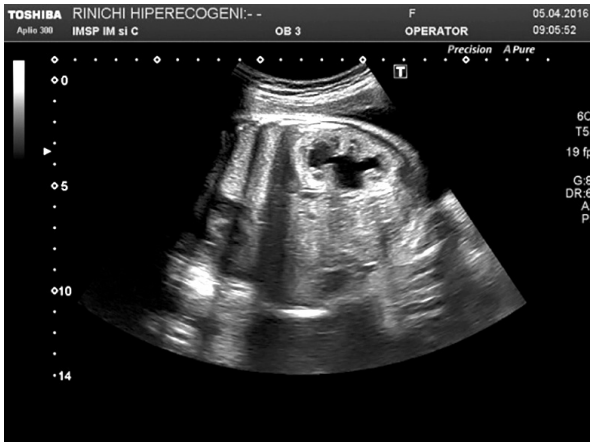


Fig. 4 and 5. Hyperecogenic kidneys.

severe cases causing postnatal terminal renal failure, leading to perinatal death, to the mildest cases, which can remain clinically undetectable over a long period of time. Ultrasound investigation is carried out in the following terms – a) at 11 – 14 weeks when can be detected the most severe abnormalities of kidney development, e. g., renal agenesis, b) at 18 – 20 weeks when can be detected most malformations with dimensions of the defect is more than 1 – 2 cm, e. g., multicystic kidney disease, multiple congenital anomalies, associated with renal malformations, renal hypoplasia associated with oligohydramnios, and c) at 30 – 34 weeks when can be detected the defects which earlier were small in dimensions, e. g., polycystic kidney disease, Potter syndrome, and other fetal RUCA. Rate of diagnosis of congenital renal malformations is 1) at 10 – 14 weeks from 3 to 10%; 2) at 20 – 24 weeks from 45 to 60%; 3) at 30 – 34 weeks from 25 to 30%, and 5) defects which are not were detected depends on the quality of the ultrasound and the nature of the defect – from 15% to 30% of all the cases of fetal RUCA. Thus, not all renal urinary malformations can be diagnosed using ultrasound, so the cases with more extensive defects are diagnosed earlier, and the dimensions of the defect have a relative significance as the surgical correction is possible, and the prognosis for the child depends primarily on the clinical significance of the affected organ/organs.

Conclusions:

1. Medical-genetic counseling and prenatal ultrasound screening are the most effective methods of diagnosis of RUCA in fetuses. Using a prenatal diagnosis from the earliest term of pregnancy allows the early detection of RUCA as well as avoiding the birth of children with severe renal urinary pathologies. This method is indicated for the prevention of the birth of children with RUCA.
2. The specification of a monitoring program for pregnant women at the antenatal stage allows the diagnosis of RUCA in the fetus in 100% of cases. The prenatal medical-genetic counseling is very important as it is facilitate understanding of the tasks assigned to this program and the specialized surgical approach of a newborn child with RUCA in the postnatal period.
3. The approach in a multidisciplinary team consisting of geneticist, obstetrician, professional in ultrasonography, urologist, and surgeon of a newborn with RUCA ensures of an effective and early treatment, as well as the choice of the optimal method for correcting congenital anomalies of the urinary system and the evaluation of immediate and long-term outcomes of treatment.

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