# Congenital anomalies: occurrence and potential risk factors

## Urođene anomalije: pojava i potencijalni faktori rizika

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**Abstract**

**Background/Aim.** Congenital malformations still represent one of the most important causes of prenatal and infant death. The study aim was to analyze occurrence, outcomes and risk factors of different types of congenital anomalies. **Methods.** The study included all pregnant women directed to Clinic of Obstetrics and Gynecology, Clinical Center of Serbia, Belgrade due to prenatally diagnosed congenital fetal anomalies during past ten years (January 1, 2008–December 31, 2017). Upon admission to our Clinic a detailed general medical and obstetrical history were taken from every patient. All women underwent genetic testing. Ultrasonography and magnetic resonance were diagnostic methods for fetal malformations confirmation. **Results.** The study included 773 pregnant women aged from 18 to 46 years. Out of registered nine different groups of fetal anomalies/malformations, the most common were malformations of the central nervous system, while majority of fetuses had combined multiple anomalies. Genetic cause for congenital anomalies was present in 25.2% of pregnancies. Medical preg-nancy abortion was performed in 71.8% of cases. Only 10.2% of pregnancies ended in term. The best outcome for children was obtained in case of gastrointestinal anomalies (52% live born). Contrary, only one child with neck and thorax malfor-mations could be saved. According to logistic regression the most important predictor of having a child with combined multiple anomalies was mother's age, while predictor of central nervous system anomalies was gestational diabetes. The signifi-cant predictor of genetic anomalies was mother's age. **Conclu-sion.** In our sample neurological congenital anomalies were the most common, although abnormalities of all organ systems were registered. Majority of pregnancies had to be discontinued due to combined multiple anomalies caused by genetic disor-ders. Older mother's age and diabetes can imply on the in-creased risk for fetal malformations.

**Key words:**
age factors; congenital abnormalities; diagnosis; incidence; pregnancy; prognosis; risk factors; ultrasonography.

**Apstrakt**

**Uvod/Cilj.** Urođene malformacije i dalje predstavljaju jedan od najvažnijih uzroka prenatalne i neonatalne smrti. Cilj rada bio je analiza pojave ishoda različitih tipova kongenitalnih anomalija. **Metode.** Studijom su bile obuhvaćene sve trudnice koje su u periodu 1. januar 2008–31. decembar 2017. godine bi-le upućene na Kliniku za ginekologiju i akušerstvo Kliničkog centra Srbije zbog prenatalno dijagnostikovanih kongenitalnih fetalnih anomalija. Po prijemu na našu Kliniku uzimani su de-taljni opšti medicinski i akušerski podaci od svake pacijentkinje. Sve trudnice su podvrgnute genetskom testiranju. Ultrazvuk i magnetna rezonanca su bili dijagnostičke metode za potvrdu malformacija fetusa. **Rezultati.** Studijom su obuhvaćene 773 trudnice koje su imale od 18 do 46 godina života. Od registro-vanih devet različitih grupa fetalnih anomalija/malformacija, najčešće su bile malformacije centralnog nervnog sistema, dok je većina fetusa imala više kombinovanih anomalija. Genetički uzrok kongenitalnih anomalija bio je prisutan u 25,2% trudno-ća. Medicinski prekid trudnoće obavljen je u 71,8% slučajeva. Samo 10,2% trudnoća je završeno u terminu. Najbolji ishod za decu dobijen je u slučajevima gastrointestinalnih anomalija (52% živorođenih). Nasuprot tome, samo jedno dete sa mal-formacijama vrata i grudnog koša se moglo spasiti. Prema logi-stičkoj regresiji najvažniji prediktor da dete ima kombinovane višestruke anomalije je bila starost majke, dok je prediktor anomalija centralnog nervnog sistema bio gestacijski dijabetes. Značajan prediktor genetskih anomalija bila je starost majke. **Zaključak.** U našem uzorku najčešće su bile neurološke kon-genitalne anomalije, iako su registrovane abnormalnosti svih organskih sistema. Većina trudnoća se morala prekinuti zbog kombinovanih višestrukih anomalija uzrokovanih genetskim poremećajima. Starije životno doba majke i dijabetes mogu ukazivati na povišen rizik od fetalnih malformacija.

**Ključne reči:**
životno doba, faktori; anomalije; dijagnoza; incidenca; trudnoća; prognoza; faktori rizika; ultrasonografija.

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## Introduction

Congenital anomalies or malformations of the fetus are disorders of the structure, behavior, function and metabolism that arose before birth [1]. They result from disturbed development and growth during the embryonic and fetal intrauterine period. Etiology can be chromosomal and genetic, infectious, medicamentous, multifactorial, etc [2].

According to the literature data the incidence of fetal anomalies is 1.5% per year. The incidence of anomalies in pregnancies ending in spontaneous abortion is 3.3%, with intrauterine fetal death is 13%, while 0.4% of fetal anomalies are diagnosed after birth [3, 4]. Infant mortality rate from congenital malformations in a period of 15 years prior to our study (1993 to 2007) in Serbia was 1.8 (confidence interval 1.5–2.1) out of which 45.1% was caused by genetic disorders [5].

Whether the developmental anomalies occurred during organogenesis (malformation) or after their initial normal organ formation (disruption and deformation) the timely diagnosis of fetal anomalies allows medical practitioners to make an appropriate decision on the further pregnancy management [2, 6]. It is necessary to detect and discontinue pregnancy with fetal anomalies incompatible with life in time, or to begin the appropriate treatment of diagnosed malformation as soon as possible to enable not only survival, but also good quality of life for the child [7].

Although recently much has been done to improve malformation early diagnosis and treatment, there is still a debate about all risk factors causing congenital anomalies. Therefore, the aim of this study was to analyze occurrence and outcomes of different types of congenital anomalies from the tertiary referral center during a ten-year period. Moreover, study aimed at examining potential predictors of congenital anomalies based on patients' characteristics and medical history data.

## Methods

Study included all consecutive pregnant women directed to the Clinic of Obstetrics and Gynecology, Clinical Center of Serbia in Belgrade due to prenatally suspected congenital fetal anomalies. Our Clinic is one of the three tertiary referral centers for medically indicated late pregnancy terminations in Serbia in charge of patients from central Serbia (Šumadija) as well as the most complex cases from the whole country. The study was approved by the Institutional Review Board. Women were prospectively included in the study during a period of ten years (from January 1, 2008 to December 31, 2017). All investigated patients signed informed consent for the study. The main inclusion criterion was prenatally verified (clinical and/or laboratory) congenital anomaly/malformation of the fetus.

Upon admission to our Clinic a detailed general medical and obstetrical history were taken from every patient regarding age, hereditary and chronic illnesses, parity, gestational complications and outcomes of previous pregnancies (pregnancy losses, previous congenital anomalies). During the examined pregnancy we registered all gestational illnesses and complications (diabetes, rhesus D – RhD immuniza-

tion) as well as the infections that could potentially cause fetal malformations [toxoplasmosis, rubella, varicella, herpes simplex virus (HSV), hepatitis B virus (HBV), cytomegalovirus (CMV), intestinal bacteria and others].

All women underwent screening for genetic abnormalities – in the first trimester (11 to 14 gestational weeks) Double test and in the second trimester (16 to 19 gestational weeks) Triple test were performed. For these tests we used Brahms Kryptor analyzer and fluorocytometric immunoassay with SsdwLab 5 software. Moreover, fetal karyotipisation was done in order to make the final diagnosis of potential genetic disorder. In case of suspected specific chromosomal numerical or structural disorders and rearrangements polymerase chain reaction (PCR) with appropriate primers was also done. Cell samples for genetic analyses were obtained by chorionic willi biopsy, amniocentesis or cordocentesis (depending on the gestational week).

Ultrasound (US) biometry and pregnancy monitoring were performed through ACCUVIX device (Samsung Medison, Seoul, Sought Korea), with 3.75 MHz abdominal and vaginal probe. Pregnancies were dated by last menstrual period and US biometric parameters. Biometrical parameters were also used for diagnosing fetal intrauterine growth restriction (IUGR). Moreover, US was used to assess amniotic fluid volume based on the deepest fluid pocket measurements (oligoamnion < 2 cm; normal fluid 2–8 cm; polyhydramnion > 8 cm). These two patological findings were specially registered as they can somethimes indicate other pregnancy complications including that fetuses have congenital anomalies.

US was the main diagnostic method for assessing fetal malformations. All examinations were performed by three obstetrics and gynecology specialists and perinatology US experts (study authors). Moreover, in some cases magnetic resonance (MR) imaging of the fetus was also done using the Siemens 1.5 Tesla Symphony apparatus. The final diagnosis as well as the decision for anomaly treatment or pregnancy termination were done in accordance with neonatologists and pediatric surgeons, members of the Congenital Anomalies/Malformations Consilium of our Clinic.

In case of minor fetal anomalies, which could be surgically corrected after birth, it was decided to continue the pregnancy and these patients were regularly checked-up throughout the second and third pregnancy trimester according to the high-risk pregnancy guidelines. The main positive pregnancy outcome assessed in the study was having liveborn children.

Contrary, if the anomaly was of genetic origin, surgically uncorrectable or incompatible with life, pregnancy was terminated after the parents signed the informed consent. We noted the method of pregnancy termination for every patient (curettage in the first or early second trimester, instillation or feticide) as well as the way of abortion/delivery (Caesarean section or vaginal delivery with or without prostaglandins PGM15 or PGE2, Foley catheter or oxytocin induction/stimulation).

We noted the week of obtaining the final diagnosis of congenital anomaly as well as the week of pregnancy termination in each case. For final malformation verification all fetuses that were not liveborn were sent to autopsy and hi-

stopathological examinations. Liveborn children were assessed by neonatologist after birth. All malformations were grouped according to the affected organ system and divided on those with and without genetic cause.

All obtained data were statistically analyzed using methods of descriptive (number, percentage, mean, standard deviation) and analytical statistics and applying the SPSS 20 software. Significance of differences between categories of assessed parameters was examined by $\chi^2$ test. Correlations of fetal anomaly type and pregnancy outcome with patients' characteristics and medical history data were tested using Spearman's correlation.

Finally, we applied multiple logistic regression to investigate the predictors of occurrence of different types of congenital anomalies based on patients' characteristics and medical history data. Moreover, we performed binary logistic regression to investigate the predictors genetic anomalies based on patients' characteristics and medical history data.

## Results

Study included 773 pregnant women aged from 18 to 46 years. Data regarding patients' age, previous parity and the gestational week when the malformation was diagnosed are presented in Table 1. Majority of women did not have any hereditary or chronic illnesses as well as pregnancy complication in previous and investigated pregnancy (Table 2).

**Table 1**

### Descriptive general data of investigated patients

| Parameters | Minimum–Maximum | Mean ± Standard deviation |
|---|---|---|
| Age (years) | 18.00–46.00 | 30.35 ± 6.35 |
| Previous parity (n) | 0.00–9.00 | 1.07 ± 1.30 |
| Live-born children up to now (n) | 0.00–6.00 | 0.63 ± 0.81 |
| Prior abortions (n) | 0.00–7.00 | 0.17 ± 0.61 |
| Prior miscarriages (n) | 0.00–4.00 | 0.23 ± 0.55 |
| Gestational month of miscarriage (n) | 0.00–7.00 | 2.30 ± 0.90 |
| Gestational week of malformation diagnosis (n) | 9.00–39.00 | 23.81 ± 7.05 |

**n - number of occurrences.**

**Table 2**

### Frequency of investigated parameters in examined patients

| Parameters | Number (%) | $\chi^2$ | $p$ |
|---|---|---|---|
| Diabetes mellitus in family | | | |
|   no | 736 (95.2) | 2033.784 | 0.001 |
|   mother | 25 (3.2) | | |
|   father | 9 (1.2) | | |
|   others | 3 (0.4) | | |
| Gestational diabetes | | | |
|   no | 758 (98.1) | 714.164 | 0.001 |
|   yes | 15 (1.9) | | |
| RhD incompatibility | | | |
|   no | 695 (89.9) | 492.483 | 0.001 |
|   yes | 78 (10.1) | | |
| RhD immunization | | | |
|   no | 772 (99.9) | 769.005 | 0.001 |
|   yes | 1 (0.1) | | |
| Infections during pregnancy | | | |
|   no infections | 728 (94.2) | 3344.684 | 0.001 |
|   toxoplasmosis | 6 (0.8) | | |
|   rubella and/or varicella | 5 (0.6) | | |
|   cytomegalovirus | 4 (0.4) | | |
|   other viruses[1] | 13 (1.7) | | |
|   intestinal bacteria | 13 (1.7) | | |
|   other rare findings[2] | 5 (0.6) | | |
| Double test findings | | | |
|   low risk | 590 (76.3) | 214.294 | 0.001 |
|   high risk | 183 (23.7) | | |
| Triple test findings | | | |
|   low risk | 371 (58.3) | 34.371 | 0.001 |
|   high risk | 265 (41.7) | | |
| Genetic abnormalities | | | |
|   no | 578 (74.8) | 1035.554 | 0.001 |
|   syndrome Down | 107 (13.8) | | |
|   other aneuploidies | 51 (6.6) | | |
|   gene mutations/rearrangements | 37 (4.8) | | |

[1]**Other viruses – Parvo B 19, HBV – hepatitis B virus, HCV – hepatitis C virus, HPV– human papilloma virus, influenca and Zika viruses;** [2]**other rare findings – Ureaplasma, Mykoplasma and Chlamydia; RhD – rhesus D.**

**Table 3**

**Ultrasonography (US)/magnetic resonance (MR) and final findings of fetal congenital anomalies/malformations**

| Parameters | Number (%) | $\chi^2$ | $p$ |
|---|---|---|---|
| US / MR findings of fetal anomalies and malformations and/or other pathologies potentially implying on anomalies | | | |
| no anomalies | 148 (19.1) | | |
| central nervous system | 226 (29.2) | | |
| neck and thorax | 41 (5.3) | | |
| cardiovascular | 85 (11.0) | | |
| gastrointestinal | 47 (6.1) | 580.142 | 0.001 |
| musculoskeletal | 38 (4.9) | | |
| urogenital | 57 (7.4) | | |
| other rare findings | 10 (1.3) | | |
| combined multiple | 70 (9.1) | | |
| intrauterine growth restriction | 26 (3.4) | | |
| Final findings of fetal anomalies and malformations | 197 (25.5) | | |
| central nervous system | 42 (5.4) | | |
| neck and thorax | 68 (8.8) | | |
| cardiovascular | 50 (6.5) | | |
| gastrointestinal | 38 (4.9) | 704.503 | 0.001 |
| musculoskeletal | 46 (6.0) | | |
| urogenital | 40 (5.2) | | |
| chromosomal without anatomy | 48 (6.2) | | |
| other rare findings | 244 (31.6) | | |

Significantly more women had low risk on screening test, both Double and Triple. However, Triple test seemed to be more reliable in our population for congenital malformation prediction as almost 40% of pregnancies were adequately recognized as in risk. US and MR as diagnostic tool for congenital malformations were very reliable as 74.3% of malformations were appropriately prenatally detected (Table 3). These imaging methods had the best results for assessment of central nervous system (CNS) anomalies. Still, in some cases no anomalies were visualized or only intrauterine growth restriction (IUGR) and abnormality in amniotic fluid volume were registered.

Nine different groups of fetal anomalies/malformations (according to organ system) were confirmed on the examinations upon pregnancy termination (Table 3). The most common once were malformations of the CNS, while majority of fetuses had combined multiple anomalies. Genetic cause for congenital anomalies was present in 25.2% of pregnancies (Table 2) out of which Down's syndrome was the most common.

When genetic abnormalities were analyzed we registered eight deletions, five duplications, six inversions, four translocations and 14 single gene polymorphysms. When aneuploidies were evaluated Turner's syndrome was registerd in eight case, Patau in eight cases, Edward's syndrome in 15 cases, Klinefelter's syndrome in seven cases, triple X in three cases, trisomies of chromosomes 8, 18 and 20 in one case each, mosaic in six cases, while in one case multiple trisomies were registered.

In patients with gestational diabetes mellitus we registered anomalies of the CNS in six cases, cardiovascular system (CVS) in two cases, gastrointestinal (GIT) in two cases (omphalocelea), while in one patient fetus had urogenital (kidney) anomalies. In four patients with gestational diabetes mellitus we registered multiple fetal anomalies out of which

in two cases fetuses had combined cystic neck hygroma with abdominal tumefactions and in remaining two cases cystic neck hygroma was combined with mediastinal tumors and generalised fetal hydrops.

Pregnancy outcomes are presented in Table 4. Medical pregnancy abortion was performed in 71.8% of cases. Only 10.2% of pregnancies ended in term. Significantly more pregnancies were ended during the second trimester. In 63 women Caesarean section had to be performed due to obstetrical indications.

**Table 4**

**Pregnancy outcomes**

| Parameters | Number (%) | $\chi^2$ | $p$ |
|---|---|---|---|
| Medical abortion | | | |
| no | 218 (28.2) | 146.920 | 0.001 |
| yes | 555 (71.8) | | |
| Curettage (I or II trimester) | | | |
| no | 455 (58.8) | 419.397 | 0.001 |
| yes | 318 (41.1) | | |
| Induced vaginal delivery | | | |
| no | 457 (59.1) | 408.290 | 0.001 |
| yes | 316 (40.0) | | |
| Caesarean section parva | | | |
| no | 712 (92.1) | 548.255 | 0.001 |
| yes | 63 (8.2) | | |
| Pregnancy termination time | | | |
| in term | 79 (10.2) | 734.389 | 0.001 |
| I trimester | 113 (14.6) | | |
| II/III trimester | 581 (75.2) | | |
| Live-born children | | | |
| no | 673 (87.1) | 424.746 | 0.001 |
| yes | 100 (12.9) | | |

In our study 12.9% (100 out of 773) of children had correctible malformations and therefore were successfully liveborn. Anomaly type and having liveborn children correlated negatively ($\rho$ = - 0.075; $p$ = 0.037). Among investigated fetuses liveborn children had all registered anomaly types. However, the majority of anomalies that were considered minor and/or tretable were those of gastrointestinal tract (mostly gastrochisis and omphalocela). The best outcome for children was obtained in case of gastroschisis omphalocele (26 out of 50 children were liveborn – 52%). Out of CNS anomalies liveborn children mostly had slight ventriculomegalia, while majority of minor urogenital anomalies in our sample were renal cysts. There were four cases of single heart anomalies that were successfully operated after delivery. Moreover, in our study there were also 16 cases of multiple anomalies that were treatable and these mostly included combined CVS anomalies. Contrary, only one child (2.4%) with malformations of the neck and thorax could be saved.

Patients age, findings of Double and Triple tests, genetic abnormalities and I trimester curettage as the pregnancy termination method correlated positively, while gestational week of diagnosis and vaginal method of delivery correlated negatively with the type of registered anomalies (Table 5). Combined multiple anomalies were more often registered in older women. These malformations were mostly on genetic basis and registered early by screening methods. Consequently, pregnancies with fetuses that had combined multiple anomalies in our sample were commonly terminated in the first trimester.

Having liveborn children with congenital anomalies correlated positively with having all previous children liveborn, gestational week of malformation diagnosis and the findings of US/MR, while it correlated negatively with patient's age, findings of Double and Triple tests, genetic abnormalities as well as the pregnancy termination time and type. So it can be seen that having healthy previous pregnancies and performing regular pregnancy check-ups that could allow early diagnosis of any gestational complications is the best way to ensure that even children with congenital anomalies can be live-born if their malformations are correctable. Conversely, genetic anomalies were the major cause of both spontaneous as well as medically induced pregnancy terminations.

Finally, we obtained a significant model for prediction of occurrence of different types of congenital anomalies based on patients' characteristics and medical history data (R = 0.412; adjusted $R^2$ = 0.613; F = 2.999; $p$ = 0.003; constant = 0.724). According to our findings the most important predictors of having a child with combined multiple anomalies were mother's age (B = 0.183), while predictor of CNS anomalies was gestational diabetes (B = -2.0303). Moreover, we obtained a significant model for prediction of genetic anomalies based on patients' characteristics and medical history data (B = 0.704; Wald = 15.572; Nagelkerke $R^2$ = 0.617; $\chi^2$ = 24.082; $p$ = 0.004; explained variance = 68.3%). The significant predictor was mother's age (constant = -5.073; B = 0.143).

**Table 5**
**Correlations of fetal anomaly type and pregnancy outcome with patients' characteristics and medical history data**

| Parameters | Anomaly type | Live-born children |
|---|---|---|
| Patients age | | |
| rho | **0.217** | **-0.138** |
| $p$ | **0.001** | **0.001** |
| Previous parity | | |
| rho | 0.029 | -0.063 |
| $p$ | 0.426 | 0.079 |
| Live-born children up to now | | |
| rho | -0.001 | **0.107** |
| $p$ | 0.979 | **0.003** |
| Prior miscarriages number | | |
| rho | 0.061 | -0.014 |
| $p$ | 0.091 | 0.704 |
| Gestational month of miscarriage | | |
| rho | -0.072 | -0.009 |
| $p$ | 0.392 | 0.914 |
| Gestational week of malformation diagnosis | | |
| rho | **-0.198** | **0.169** |
| $p$ | **0.001** | **0.001** |
| Diabetes mellitus in family | | |
| rho | -0.056 | -0.014 |
| $p$ | 0.119 | 0.693 |
| Gestational diabetes | | |
| rho | -0.042 | 0.002 |
| $p$ | 0.242 | 0.963 |
| RhD incompatibility | | |
| rho | 0.050 | -0.001 |
| $p$ | 0.166 | 0.974 |
| RhD immunization | | |
| rho | 0.044 | -0.014 |
| $p$ | 0.225 | 0.700 |
| Infections during pregnancy | | |
| rho | 0.031 | 0.051 |
| $p$ | 0.392 | 0.154 |
| Double test findings | | |
| rho | **0.324** | **-0.160** |
| $p$ | **0.001** | **0.001** |
| Triple test findings | | |
| rho | **0.145** | **-0.082** |
| $P$ | **0.000** | **0.022** |
| Genetic abnormalities | | |
| Rho | **0.496** | **-0.162** |
| $P$ | **0.001** | **0.001** |
| US/MR findings | | |
| Rho | **0.128** | **0.071** |
| $P$ | **0.001** | **0.050** |
| Medical abortion | | |
| Rho | -0.018 | **-0.615** |
| $P$ | 0.612 | **0.001** |
| Curettage | | |
| rho | **0.112** | **-0.323** |
| $p$ | **0.002** | **0.001** |
| Induced vaginal delivery | | |
| rho | **-0.075** | **-0.219** |
| $p$ | **0.036** | **0.001** |
| Caesarean section parva | | |
| rho | 0.033 | -0.013 |
| $p$ | 0.363 | 0.724 |
| Pregnancy termination time | | |
| rho | 0.001 | **-0.416** |
| $p$ | 0.972 | **0.001** |

RhD – rhesus D; US – ultrasonography; MR – magnetic resonance.
**Note: Statistically significant values are bolded.**

**Discussion**

Worldwide investigations have shown that occurrence of congenital anomalies varies greatly among countries. The prevalence of congenital anomalies according to literature data ranges from as low as 1.07% in Japan and as high as 4.3% in Taiwan [8, 9]. Major anomalies, which significantly affect the development and quality of life of a human individual, are present in 2%–3% of newborn children, while another 2%–3% of malformations are diagnosed by the age of five [10, 11]. They are one of the main causes of childhood deaths (up to 20%–25% of cases). Contrary, minor anomalies (skin lesions, small ears or a narrow gap between the eyebrows) occur in about 15% of newborns, they do not affect health, but their presence can indicate at the same time the existence of some major malformations [1, 12]. Furthermore, frequency and structure of different types of congenital anomalies depend on the investigated population. Specific studies have registered the predominance of different congenital anomalies, however, based on all available literature data the most common ones are usually neurologic, cardiac, gastrointestinal and musculoskeletal malformations. Abnormalities on all other organ systems are less often reported [13, 14].

Differences found in congenital anomalies rates in different countries and studies could be based on actual variations among assessed populations or due to different anomalies definitions or study methods [7, 15]. Additionally, inclusion of stillbirths, prenatally diagnosed cases and pregnancy terminations increase significantly the overall prevalence of children with congenital anomalies. Moreover, in less developed countries there are no registries of children with malformations or the data are poorly documented and insufficient [13, 16]. Consequently, epidemiologists are often reluctant to present the total prevalence of congenital anomalies in certain countries and populations [9]. Nevertheless, congenital malformations, taken collectively, are fairly common, and account for a disproportionate share of adverse perinatal outcomes. Therefore, in the year 1979, a network of population-based registries, European Surveillance of Congenital Anomalies (EUROCAT) was made in order to conduct epidemiological surveillance of congenital anomalies in Europe [4]. Cli-nicians and researchers are encouraged to use data from this and other reliable population-based registries, while all countries should take participation in active registration and reporting of congenital anomalies [3].

In our study of prenatally diagnosed congenital malformations in the population from central Serbia the most common single organ system anomalies were registered on CNS, while numerous children also had multiple combined anomalies. Majority of these multiple anomalies were due to genetic syndromes (mostly Down syndrome). In our sample only 12.9% of children were liveborn. This was the first study in Serbian population that made prediction models for congenital anomalies based on patients' characteristics and medical history data. According to logistic regression the most important predictors of having a child with combined multiple anomalies were mother's age, while gestational diabetes was associated with CNS anomalies. The significant predictor of genetic anomalies was mother's age.

**Conclusion**

In our sample from central Serbian referral tertiary clinic congenital anomalies of CNS were the most common single system anomalies, although malformations of all organ systems were registered. Majority of pregnancies had to be discontinued due to combined multiple anomalies caused by genetic disorders. Older mother's age and diabetes can imply on the high risk for fetal malformations. Regular pregnancy check-ups can allow early diagnosis of any gestational complications and ensure that even children with congenital anomalies can be liveborn if their malformations are correctable. Construction and regular updating of a detailed (including all patients data) congenital anomalies registry in Serbia is necessary and might help clinicians and enhance further investigations of this issue.

**Conflict of interest**

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