

Changes in the Detection and Management of Foetal Trisomies over Time

Detektion und Management von fetalen Trisomien im Wandel der Zeit



Authors

Natalia Prodan, Markus Hoopmann, Harald Abele, Philipp Wagner, Diethelm Wallwiener, Sara Brucker, Karl Oliver Kagan

Affiliation

Universitäts-Frauenklinik Tübingen, Tübingen, Germany

Key words

trisomy, cell-free DNA, first trimester screening, termination of pregnancy

Schlüsselwörter

Trisomie, zellfreie DNA, Ersttrimester-Screening, Schwangerschaftsabbruch

received 6. 5. 2018

revised 18. 6. 2018

accepted 25. 6. 2018

Bibliography

DOI <https://doi.org/10.1055/a-0648-5374>

Geburtsh Frauenheilk 2018; 78: 853–858 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

Correspondence

Prof. Dr. Karl Oliver Kagan
Universitäts-Frauenklinik Tübingen
Calwerstraße 7, 72076 Tübingen, Germany
KOKagan@gmx.de

Deutsche Version unter:
<https://doi.org/10.1055/a-0648-5374>

ABSTRACT

Introduction This study investigates whether the time of diagnosis of foetal trisomy 21/18/13 and the frequency of termination of pregnancy have changed in the past 10 years.

Material and Methods Retrospective study at the Tübingen University Centre for Women's Health in which the cases with ante- and postnatal diagnosis of trisomy were investigated. A prerequisite was that the patients be examined in the antenatal medicine department. The time of diagnosis, the frequency of termination of pregnancy and the gestational age in the case of a termination were assessed.

Results Between 2007 and 2017, trisomy 21/18/13 was diagnosed in 498 fetuses and newborns. In 311 of the fetuses or newborns, trisomy 21 was identified; in 134, trisomy 18; and in 53, trisomy 13. The median gestational age at diagnosis in the case of fetuses with trisomy 21 was between 14.4 and 13.6 weeks of pregnancy. The rate of pregnancy terminations increased slightly from 66.7% between 2007 and 2010 to 75.5% between 2015 and 2017. The median gestational age at the time of termination remained constant at 14.9 and 15.0 weeks of pregnancy respectively. The median gestational age at diagnosis in the case of fetuses with trisomy 18/13 was between 13.6 and 14.6 weeks of pregnancy during the examination period. The percentages of affected pregnancies which were terminated in the three time periods increased slightly from 57.4 to 69.0%. The gestational age remained unchanged in this case at 15.0 and 15.1 weeks of pregnancy respectively.

Conclusion The time of intrauterine diagnosis of trisomy 21/18/13 has not changed in the past 10 years. The frequency of termination of a pregnancy increased slightly and the time of termination remained unchanged.

ZUSAMMENFASSUNG

Einleitung In dieser Arbeit soll untersucht werden, ob sich der Zeitpunkt der Diagnose einer fetalen Trisomie 21/18/13 und die Häufigkeit eines Schwangerschaftsabbruchs in den vergangenen 10 Jahren geändert hat.

Material und Methoden Retrospektive Studie an der Universitäts-Frauenklinik Tübingen, bei der die Fälle mit prä- und postnataler Diagnose einer Trisomie untersucht wurden. Voraussetzung war, dass die Patientinnen in der pränatalmedizinischen Abteilung gesehen wurden. Untersucht wurde der Zeitpunkt der Diagnose, die Häufigkeit eines Schwangerschaftsabbruchs und das Gestationsalter bei einem Abbruch.

Ergebnisse Zwischen 2007 und 2017 wurde bei 498 Feten bzw. Neugeborenen eine Trisomie 21/18/13 diagnostiziert. Bei 311 der Feten bzw. Neugeborenen wurde eine Trisomie 21 festgestellt, bei 134 eine Trisomie 18 und bei 53 eine Trisomie 13. Der mediane Zeitpunkt der Diagnose bei Feten mit Trisomie 21 lag zwischen 14,4 und 13,6 SSW. Die Rate an

Schwangerschaftsabbrüchen stieg leicht an von 66,7% zwischen 2007 und 2010 auf 75,5% zwischen 2015 und 2017. Das mediane Gestationsalter zum Zeitpunkt des Abbruchs blieb dabei konstant bei 14,9 bzw. 15,0 SSW. Der mediane Zeitpunkt der Diagnose bei Feten mit Trisomie 18/13 lag im Untersuchungszeitraum zwischen 13,6 und 14,6 SSW. Der Anteil der betroffenen Schwangerschaften, die in den 3 Zeiträumen abgebrochen wurden, stieg leicht von 57,4 auf

69,0%. Das Gestationsalter blieb dabei aber unverändert bei 15,0 bzw. 15,1 SSW.

Schlussfolgerung Der Zeitpunkt der intrauterinen Diagnose einer Trisomie 21/18/13 hat sich in den vergangenen 10 Jahren nicht verändert. Die Häufigkeit eines Schwangerschaftsabbruchs stieg leicht an, wobei der Zeitpunkt des Abbruchs unverändert blieb.

Introduction

In recent years, antenatal aneuploidy screening has evolved considerably [1, 2].

In the 1990s, the antenatal risk evaluation was still primarily based on the maternal age risk [3]. In the following years, with the introduction of the combined first trimester screening (FTS), screening using only the maternal age risk was largely replaced [4]. The advantage primarily concerned the significantly higher test quality. Using FTS, about 90–95% of fetuses with trisomy 21 and 95% of fetuses with trisomy 18 and 13 could be detected, while the detection rate based on maternal age was only around 50% for trisomy 21 and 10% for trisomy 18/13 [5–7]. Even more significant was the decrease in the false-positive rate from 25 to 5%. Hui et al. demonstrated for Australia that amniocenteses significantly decreased as a consequence of the introduction of FTS starting in 2000 [8].

In recent years, a new paradigm shift can be observed with the introduction of cell-free DNA (cfDNA) in antenatal diagnostics. Using this screening method, about 99% of pregnancies with trisomy 21 and 93% and 84% of pregnancies with trisomy 18 and 13, respectively, can be detected with a false-positive rate of about 0.05% in each case [9]. This method was initially regarded with reserve due to its high cost, but now much more affordable prices have led to a steadily growing importance in antenatal screening for trisomy 21. As a consequence, a study has investigated whether cfDNA analysis in combination with a detailed ultrasound examination could also be used as a primary screening strategy and demonstrated it can be used as such [10]. Along with the improved test quality, the simple handling of the cfDNA analysis is advantageous since it involves only a blood draw and counselling as defined by the German Genetic Diagnostics Act (GenDG).

With the introduction of FTS, the earliest possible time of diagnosis of a chromosome disorder has been shifted from the second to the first trimester. The cfDNA analysis enables an even earlier risk assessment. It is feared that as a result of aneuploidy screening occurring earlier and becoming less complicated, the attitude towards pregnancies with a foetal chromosome disorder will change and the rate of pregnancy terminations will increase. A recently published meta-analysis by Hill et al. investigated patient's attitude regarding terminating a pregnancy with trisomy 21 identified using cfDNA analysis. Interestingly, the percentage of terminations remained the same or even decreased in comparison to the pre-cfDNA era [11].

This work is intended to investigate whether in a large perinatal centre – providing healthcare regionally and transregionally – the

time of diagnosis of a foetal trisomy 21, 18 and 13 as well as the frequency of pregnancy terminations has changed in the past 10 years. The 10-year period is characterised by the increased use of the first-trimester screening and, for the past several years, also through screening using cfDNA analysis.

Material and Methods

Description of the study collective

About 12 000 patients are seen annually in the Department of Antenatal Medicine of the Tübingen University Hospital. A total of four physicians, two of whom are DEGUM III-certified, work in the department. Patients are referred for screening examinations and for second opinion, diagnosis, counselling and management of abnormal findings.

The entire spectrum of screening examinations is offered. Since 2012, this has also included cfDNA analysis. All pregnant women with an abnormal ultrasound, cfDNA or other abnormal screening finding are offered an invasive diagnostic procedure, generally amniocentesis or chorionic villus sampling. If this is not desired, postnatal diagnostic testing is indicated.

The pregnancy is not terminated alone on the basis of suspected trisomy 21. This always requires karyotyping beforehand. If trisomy 18 or 13 is suspected, the pregnancy may be terminated due to multiple deformities and the resulting stress. In general, an attempt is also made in these cases to perform karyotyping before terminating the pregnancy. If this is not possible, post-mortem karyotyping is always performed.

Pregnancy terminations are performed without any time restriction. Foeticide is performed beforehand, if necessary. If the patient decides to continue the pregnancy, the newborn is cared for according to standard care in the case of trisomy 21. In the case of newborns with trisomy 18 and 13, palliative care or, in isolated cases, maximum care is discussed.

If the delivery takes place at another birth centre, the birth data and karyotype are subsequently entered into the Viewpoint database.

All patients who are referred for termination of pregnancy according to section 218a German Penal Code (StGB) para.2 are seen and counselled beforehand in the Department of Antenatal Medicine.

All information collected is stored in the digital Viewpoint database. In addition to the ultrasound examinations, this also includes findings from the screening tests as well as those of the

► **Table 1** Trisomy 21 cases. The table indicates – divided according to the examination period – the number of managed cases with the chromosomal disorder, the mean maternal age and gestational age at diagnosis, the percentage of pregnancies which were terminated, and the gestational age at the time the pregnancy was terminated. In addition, the percentage of pregnancies in which a cell-free DNA analysis and an invasive diagnostic procedure were performed is shown.

	2007–2010 (3 years)	2011–2014 (3 years)	2015–2017 (2 years)
Ante- and postnatally diagnosed fetuses and newborns with trisomy 21, n	81	120	110
Maternal age at diagnosis Years, median (IQR)	37.3 (35.1–39.7)	36.1 (32.2–39.9)	37.2 (35.2–39.7)
Cell-free DNA analysis, n (%)	0 (0)	3 (2.5)	28 (25.5)
Diagnostic puncture, n (%)	76 (93.8)	101 (84.2)	106 (96.4)
Gestational age at diagnosis* WOP, median (IQR)	14.4 (12.9–16.8)	13.6 (12.6–15.7)	13.9 (12.9–16.6)
Up to 13 + 6 WOP, n (%)	41 (50.6)	64 (53.3)	63 (57.3)
14 + 0 to 17 + 6 WOP, n (%)	24 (29.9)	20 (16.7)	29 (26.4)
18 + 0 to 22 + 6 WOP, n (%)	4 (4.9)	11 (9.2)	9 (8.2)
After 23 + 0 WOP, n (%)	7 (8.6)	5 (5.0)	5 (4.5)
Post partum, n (%)	5 (6.2)	19 (15.8)	4 (3.6)
Termination of pregnancy n (%) [95% CI]	54 (66.7 [55.3–76.8])	82 (68.3 [59.2–76.2])	83 (75.5 [66.3–83.1])
Gestational age termination of pregnancy WOP, median (IQR)	14.9 (13.9–18.1)	15.0 (13.7–16.9)	14.9 (13.9–18.3)

* The diagnosis was made using ante- or postnatal karyotyping.
IQR = 25–75% interquartile range, n = number, WOP = weeks of pregnancy

ante- and postnatal karyotyping. In addition, all pregnancy terminations are noted according to section 218a StGB para. 2.

A query of the Viewpoint database was performed for this study in order to find the pregnancies in which foetal trisomy 21, 18 and 13 were diagnosed ante- and postnatally and which were seen in the Department of Antenatal Medicine. The maternal age and gestational age at the time of suspicion and at the time of diagnosis, the test method, and the outcome of the pregnancy were queried.

Statistical analysis

All results were indicated as the median with the interquartile range or as a percent of the respective initial population. The percentage of pregnancy terminations per examination interval was compared by looking at the 95% confidence interval. In the case of overlapping confidence intervals, a nonsignificant result is assumed. The gestational age at the time of termination of the pregnancy in the 2007–2010 group was compared with the gestational age of the 2015–2017 group using a Mann-Whitney U test. A normal distribution was excluded beforehand using the Shapiro-Wilk test. The significance level was < 0.05.

Results

Demographic characteristics

Between 2007 and 2017, trisomy 21, 18 or 13 were diagnosed at the antenatal centre of the Tübingen University Hospital in

498 fetuses and newborns who were examined in the Department of Antenatal Medicine. Trisomy 21 was identified in 311 (62.4%) of the fetuses or newborns, trisomy 18 was identified in 134 (26.9%), and trisomy 13 was identified in 53 (10.6%).

For the subsequent analysis, the pregnancies with foetal trisomy 18 and 13 were analysed together.

► **Tables 1** and **2** summarise the time of diagnosis of trisomy 21 or trisomy 18/13, the examinations performed at the University Women's Hospital, and the outcome of the pregnancies. The results are shown separately for the examination periods of 2007–2010, 2011–2014 and 2015–2017.

Trisomy 21

Overall, a steady increase in the diagnosed cases with foetal trisomy 21 can be observed.

The median gestational age at diagnosis using karyotyping was between 14.4 and 13.6 weeks of pregnancy. Half of the cases were diagnosed before 13 + 6 weeks of pregnancy, with a slightly increasing trend.

The percentage of trisomy 21 pregnancies in which a cell-free DNA analysis was performed increased over the course of the three investigation periods from 0 to 25.5%. 91.0% of the pregnant women with foetal trisomy 21 decided to undergo an invasive diagnostic procedure due to an increased risk, 8.4% decided against a puncture, and in two women (0.6%), no increased risk was presumed during the pregnancy. Changes over the course of the investigation period cannot be identified.

► **Table 2** Trisomy 18 and 13 cases. The table indicates – divided according to the examination period – the number of managed cases with the chromosome disorder, the mean maternal age and gestational age at diagnosis, the percentage of pregnancies which were terminated, and the gestational age at the time the pregnancy was terminated. In addition, the percentage of pregnancies in which a cell-free DNA analysis and an invasive diagnostic procedure were performed is shown.

	2007–2010 (3 years)	2011–2014 (3 years)	2015–2017 (2 years)
Ante- and postnatally diagnosed fetuses and newborns with trisomy 13/18	47	69	71
Maternal age at diagnosis Years, median (IQR)	38.5 (34.0–40.5)	35.8 (33.4–39.9)	36.2 (33.0–40.2)
Cell-free DNA analysis, n (%)	0 (0)	1 (1.4)	3 (4.2)
Diagnostic puncture, n (%)	42 (89.4)	66 (95.7)	67 (94.4)
Gestational age at diagnosis* WOP, median (IQR)	13.8 (12.4–21.9)	14.6 (12.4–20.6)	13.6 (12.6–18.1)
Up to 13 + 6 WOP, n (%)	24 (51.1)	35 (50.7)	41 (57.7)
14 + 0 to 17 + 6 WOP, n (%)	2 (4.3)	11 (15.9)	10 (14.1)
18 + 0 to 22 + 6 WOP, n (%)	8 (17.0)	10 (14.5)	11 (15.5)
After 23 + 0 WOP, n (%)	8 (17.0)	11 (15.9)	7 (9.9)
Post partum, n (%)	5 (10.6)	2 (2.9)	2 (2.8)
Termination of pregnancy n (%) [95% CI]	27 (57.4 [42.2–71.7])	45 (65.2 [52.8–76.3])	49 (69.0 [56.9–79.5])
Gestational age at termination of pregnancy WOP, median (IQR)	15.1 (13.6–21.0)	15.0 (13.3–21.1)	15.1 (13.4–18.0)

* The diagnosis was made using ante- or postnatal karyotyping.
IQR = 25–75% interquartile range, n = number, WOP = weeks of pregnancy

► **Table 3** Pregnancy terminations in the case of foetal trisomy 13/18 and 21 as a function of gestational age at diagnosis.

Time of diagnosis	2007–2010 (3 years)	2011–2014 (3 years)	2015–2017 (2 years)
Up to 13 + 6 WOP, n (%)*	49 (75.4)	82 (82.8)	85 (81.7)
14 + 0 to 17 + 6 WOP, n (%)*	20 (76.9)	26 (83.9)	31 (79.5)
18 + 0 to 22 + 6 WOP, n (%)*	10 (83.3)	15 (71.4)	14 (70.0)
After 23 + 0 WOP, n (%)*	2 (13.3)	4 (23.5)	2 (16.7)

* Percentage of pregnancies terminated out of all pregnancies with diagnosed chromosome disorder
n = number, WOP = weeks of pregnancy

The rate of pregnancy terminations increased slightly, from 66.7% between 2007 and 2010 to 75.5% between 2015 and 2017. However, the increase was not significant. The median gestational age at the time of the termination remained constant at 14.9 and 15.0 weeks of pregnancy (no significant change between 2007–2010 to 2015–2017, $p = 0.469$).

Trisomy 18 und 13

A similar trend is seen in the case of pregnancies with foetal trisomy 18/13 (► **Table 2**). The number of diagnosed chromosome disorders increased from 47 to 71 cases per examination period.

After an increased risk was identified, 89.4 to 94.4% of the patients decided to undergo a diagnostic test. The median gestational age at diagnosis using karyotyping was between 13.6 and 14.6 weeks of pregnancy. The percentage of diagnoses before

13 + 6 weeks of pregnancy increased over the course of the examination periods from 51.1 to 57.7%, while diagnoses after 23 + 6 weeks of pregnancy decreased from 17.0 to 9.9%.

The percentage of pregnancies affected which were terminated in the three time periods likewise increased slightly but not significantly from 57.4 to 69.0%. However, the gestational age at termination remained unchanged at 15.0 and 15.1 weeks of pregnancy (no significant change between 2007–2010 to 2015–2017, $p = 0.760$). The cell-free DNA analysis was not of importance in this collective.

Percentage of pregnancies terminated after diagnosis

► **Table 3** shows the percentage of pregnancies terminated in the case of foetal trisomy 21, 18 and 13 as a function of the gestational age at diagnosis. While most pregnancies were terminated prior

to 23 + 0 weeks of pregnancy, most patients after 23 + 0 weeks of pregnancy decided against terminating the pregnancy. No clear trend can be identified when comparing the three examination periods.

A cfDNA analysis was performed in 35 pregnancies. In this group, 23 (65.7%) pregnancies were terminated. In the group of pregnancies without cfDNA analysis, the termination rate was similarly high (317 [68.5%] out of 463 cases).

Discussion

In this study, the gestational age at diagnosis of trisomy 21, 18 or 13, the frequency of termination of pregnancy in the case of a corresponding chromosome disorder, and the gestational age at the time the termination was performed were investigated. This demonstrated a significant increase in diagnosed cases in the past ten years. The median gestational age at diagnosis was around 14 weeks of pregnancy in the entire examination period. The rate of terminations increased slightly but not significantly from 66.7 to 75.5% for pregnancies with trisomy 21 and from 57 to 69% for pregnancies with trisomy 18 and 13. The gestational age in the case of a termination remained unchanged.

Boyed et al. investigated the frequency of pregnancies terminated following antenatal diagnosis of trisomy 21 in 19 Eurocat centres in Europe from 2002 to 2004. The rates varied between 76 and 100% and were 96% in the German centres. The diagnosis was made on average at 15 weeks of pregnancy [12]. In a study from Japan, 94% of pregnancies with trisomy 21 were terminated. In the case of trisomy 18 and 13, the rates were 85 and 72% [13]. Also, in the study from Hume et al. from the USA which included the years from 2005 to 2014, the rate of pregnancies terminated in the case of trisomy 21 was 94% [14].

Interestingly more women chose to continue the pregnancy in the case of trisomy 18 or 13 than in the case of pregnancies with trisomy 21.

This is presumably due to the option for accompanying palliative care in the case of pregnancies with trisomy 18 and 13.

Hill et al. summarised the results of 14 studies which investigated the rate of termination of pregnancy before and after the introduction of the cfDNA analysis. Depending on the study, the termination rate before the introduction of the cfDNA analysis was between 67 and 96%. This rate did not change with the introduction of cfDNA analysis [11]. With regard to the absolute frequency of pregnancy terminations in the case of trisomy 21, our own data are concordant with the results from Hill et al. In contrast to this, a slight increase in terminations of pregnancy could be observed in our study in previous years. Whether this is a reflection of a changing attitude towards children with trisomy 21 or actually represents the result of the early screening methods is a question which cannot be definitively answered.

However, the time of diagnosis of the chromosome disorder has fundamentally not changed, despite the introduction of cell-free DNA analysis and was at 13 to 14 weeks of pregnancy on average. This likely demonstrates the already longstanding, broad acceptance of FTS in Germany. In the study by Hume et al. from the USA, the gestational age upon diagnosis of a trisomy 21 fell from 16 to 12 weeks of pregnancy between 2005 and 2014. The

authors divided the time into three periods in which FTS was available in all periods and the cfDNA analysis was available in the last period starting in 2012 [14].

Even if pregnancy terminations are fundamentally the subject of controversy, there is consensus that they should take place as early as possible in the pregnancy. In contrast to the first trimester, termination of pregnancy in the 2nd and 3rd trimester involves far more complications. Bartlett et al. investigated the mortality rate in pregnancy terminations between 1988 and 1997 in the USA. Overall, the rate was 0.7 per 100 000 terminations and increased by 38% per week starting at the 8th week of pregnancy [15]. Mark et al. investigated the morbidity rate in surgical terminations in the first and second trimester as a function of the maternal body mass index [16]. Once again, this revealed an elevated rate of complications in the second trimester in comparison to the first trimester and this rate rose even further with patients' increasing overweight. The psychological burden also increased as the gestational age increased [17]. This applies in particular in the case of a situation involving post-traumatic stress [18].

Our study is based on the data from a single university hospital. In this respect, it could be argued that they are not representative. However, since the Tübingen University Center for Women's Health has an obligation to provide regional care and it also functions as a transregional reference centre, generally valid conclusions can be drawn from the data. An advantage is that each pregnant woman with foetal trisomy is seen in the Department of Antenatal Medicine – independent of gestational age and whether the pregnancy is continued or ends in a termination. In addition, we endeavour to look after all pregnancies until the end so that we are informed of the outcome of all affected pregnancies. It should be critically mentioned that a portion of the pregnant women with an abnormal cfDNA analysis decide within the first 12 weeks after conception to terminate the pregnancy in accordance with section 218a para.1 StGB (period during which termination of pregnancy is legal). These patients forego clarification by means of invasive diagnostic procedures and indicate psychological stress as the reason for terminating the pregnancy. A statement regarding the frequency is unfortunately not possible.

In summary, we were able to show in this study that the number of trisomy 21 and also trisomy 18/13 diagnoses has increased in recent years. However, the frequency of pregnancy terminations increased only slightly. The time of the diagnosis and the terminations also did not change.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] Kagan KO, Sonek J, Wagner P et al. Principles of first trimester screening in the age of non-invasive prenatal diagnosis: screening for chromosomal abnormalities. *Arch Gynecol Obstet* 2017; 296: 645–651
- [2] Kagan KO, Sonek J, Wagner P et al. Principles of first trimester screening in the age of non-invasive prenatal diagnosis: screening for other major defects and pregnancy complications. *Arch Gynecol Obstet* 2017; 296: 635–643

- [3] Cuckle H, Maymon R. Development of prenatal screening—A historical overview. *Semin Perinatol* 2016; 40: 12–22
- [4] Snijders RJ, Johnson S, Sebire NJ et al. First-trimester ultrasound screening for chromosomal defects. *Ultrasound Obstet Gynecol* 1996; 7: 216–226
- [5] Santorum M, Wright D, Syngelaki A et al. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. *Ultrasound Obstet Gynecol* 2017; 49: 714–720
- [6] Wagner P, Sonek J, Hoopmann M et al. First-trimester screening for trisomies 18 and 13, triploidy and Turner syndrome by detailed early anomaly scan. *Ultrasound Obstet Gynecol* 2016; 48: 446–451
- [7] Abele H, Wagner P, Sonek J et al. First trimester ultrasound screening for Down syndrome based on maternal age, fetal nuchal translucency and different combinations of the additional markers nasal bone, tricuspid and ductus venosus flow. *Prenat Diagn* 2015; 35: 1182–1186
- [8] Hui L, Muggli EE, Halliday JL. Population-based trends in prenatal screening and diagnosis for aneuploidy: a retrospective analysis of 38 years of state-wide data. *BJOG* 2016; 123: 90–97
- [9] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nicht-invasive Pränataldiagnostik zur Bestimmung des Risikos autosomaler Trisomien 13, 18 und 21 bei Risikoschwangerschaften. Online: <https://www.iqwig.de/de/projekte-ergebnisse/projekte-301/nichtmedikamentoese-verfahren/s-projekte/s16-06-nicht-invasive-praenataldiagnostik-zur-bestimmung-des-risikos-autosomaler-trisomien-13-18-und-21-bei-risikoschwangerschaften.7776.html>; last access: 12.06.2018
- [10] Kagan KO, Sroka F, Sonek J et al. First-trimester risk assessment based on ultrasound and cell-free DNA vs. combined screening: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2018; 51: 437–444
- [11] Hill M, Barrett A, Choolani M et al. Has noninvasive prenatal testing impacted termination of pregnancy and live birth rates of infants with Down syndrome? *Prenat Diagn* 2017; 37: 1281–1290
- [12] Boyd PA, DeVigan C, Khoshnood B et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. *BJOG* 2008; 115: 689–696
- [13] Nishiyama M, Sekizawa A, Ogawa K et al. Factors affecting parental decisions to terminate pregnancy in the presence of chromosome abnormalities: a Japanese multicenter study. *Prenat Diagn* 2016; 36: 1121–1126
- [14] Hume H, Chasen ST. Trends in timing of prenatal diagnosis and abortion for fetal chromosomal abnormalities. *Am J Obstet Gynecol* 2015; 213: 545.e1–545.e4
- [15] Bartlett LA, Berg CJ, Shulman HB et al. Risk factors for legal induced abortion-related mortality in the United States. *Obstet Gynecol* 2004; 103: 729–737
- [16] Mark KS, Bragg B, Talaie T et al. Risk of complication during surgical abortion in obese women. *Am J Obstet Gynecol* 2018; 218: 238.e1–238.e5
- [17] Coleman PK, Coyle CT, Rue VM. Late-term elective abortion and susceptibility to posttraumatic stress symptoms. *J Pregnancy* 2010; 2010: 130519
- [18] Davies V, Gledhill J, McFadyen A et al. Psychological outcome in women undergoing termination of pregnancy for ultrasound-detected fetal anomaly in the first and second trimesters: a pilot study. *Ultrasound Obstet Gynecol* 2005; 25: 389–392