Prenat Cardio 2021; 11(1): 24–28
DOI: https://doi.org/10.5114/pcard.2021.112406
Received: 21.01.2022
Accepted: 11.02.2022

Prenatal Cardiology
www.termedia.pl/Journal/Prenatal_Cardiology

Review paper

The gender of the fetus should be included in the prenatal ultrasound – echocardiographic examination reports in tertiary centres in 2021 – recommendations from the Polish Prenatal Cardiology Society

Kacper Deska[1], Iwona Strzelecka[2], Julia Murlewska[3], Krzysztof Preis[4], Maria Respondek-Liberska[2,3]

[1]Student's Scientific Association Prenatal Cardiology, Medical University of Lodz, Poland
[2]Department of Diagnosis and Prevention of Fetal Malformations, Medical University of Lodz, Poland
[3]Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz, Poland
[4]Department of Obstetrics, Medical University of Gdansk, Poland

Abstract

The following paper is a review of research and a summary of the latest publications concerning examples of fetal sex congenital defects and their diagnostic problems with the assessment of the need to focus on fetus gender in prenatal ultrasound exams in referral centres. Determining the sex of the fetus may be of fundamental importance. However, so far it has been recommended only in Danish and Scandinavian guidelines. Defects of the genitourinary system are identifiable in prenatal tests and can coincide with other defects, including not only abdominal defects but also heart defects. Functional disorders within the external genitalia may be a clinical manifestation of heart failure and ongoing intrauterine infections. On the basis of the currently available research studies in the field of perinatology and paediatrics, we came to the conclusion that the determination of fetal sex should be carried out each time in prenatal ultrasound examinations at the reference centre.

Key words: fetal sex, ultrasound prenatal diagnosis, prenatal cardiology.

Based on the lecture of Prof. M. Respondek-Liberska presented during the online III Conference Cardio-Prenatal Poland, Lodz, 22-23 May 2021 (link to the lectures: https://youtu.be/GWMoe2qTzGw)

Corresponding author:
Dr Iwona Strzelecka
Department of Diagnosis and Prophylaxis
of Congenital Malformations
Medical University of Lodz
Rzgowska 281/289
93-345 Lodz, Poland
e-mail: i.j.strzelecka@gmail.com

Is the sex of the fetus important for a pregnant woman?

There are few publications dealing with this subject. In 2010, Maaji et al. [1], based on a conducted survey, confirmed what the authors of this publication have noticed in everyday practice – that a vast majority of pregnant women (over 94% of respondents in the survey) want to know what gender their offspring will be. The percentage of pregnant women wishing to know the sex of fetuses varies depending on the country in

This is an Open Access journal, all articles are distributed under the terms of the Creative Commons Attribution-Noncommercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0). License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

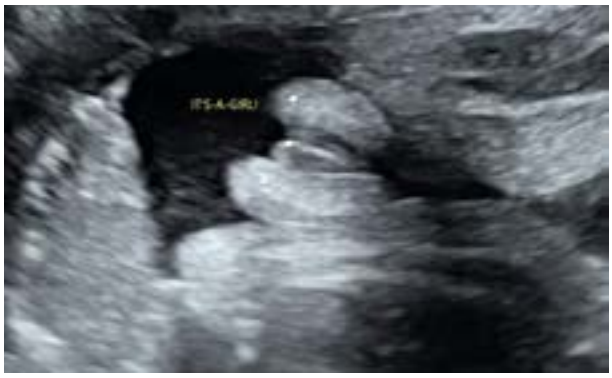

Figure 1. Female fetus in ultrasound at the 20th week of pregnancy

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

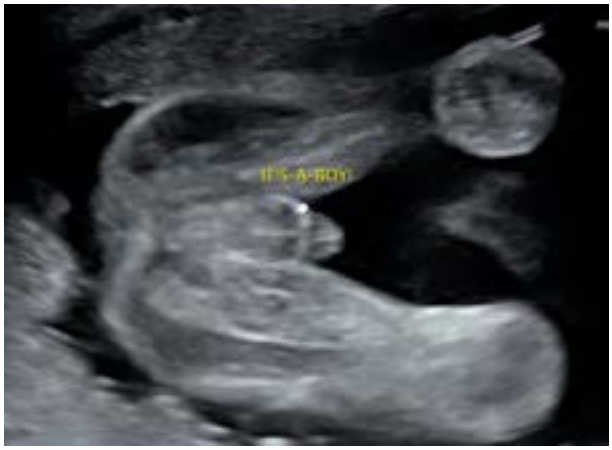

Figure 2. Male fetus in ultrasound at the 20th week of pregnancy

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

which the survey is conducted [1-3]. However, most of the currently published studies indicate that women want to know the sex of their baby at the stage of pregnancy. A Swedish study of 2018 [3] shows additionally that the majority of couples deciding to have a child had previously talked about its gender, and some of them (approx. 5%) were also interested in the possible choice of gender.

Is fetal gender determination relevant for the ultrasound/ECHO investigator and for the obstetrician managing the pregnancy?

The answer is not unequivocal. Neither Polish nor American gynaecological and obstetric guidelines contain an obligation to determine the sex of the fetus during prenatal examinations. However, in 2019, the Guidelines for Prenatal Fetal Testing of the Danish Society of Fetal Medicine and the Nordic Federation of Societies of Obstetrics and Gynaecology introduced a significant change in the aspect of prenatal sex assessment. Accordingly, determining the sex of the fetus is an integral part of prenatal testing carried out in the second trimester of pregnancy for the detection of congenital defects in the fetus [4]. The aforementioned recommendations do not indicate the need to assess the sex of the fetus in the first trimester examinations. These are the first guidelines in the world to change the approach to gender determination during prenatal testing.

Fetal gender

During prenatal tests, genetic and phenotypic gender can be distinguished. Phenotypic sex is determined by the examining ultrasound specialist based on the appearance of the external genital organs (Figures 1, 2). Genetic sex requires invasive tests such as trophoblast biopsy amniocentesis, cordocentesis, or free fetal DNA in the maternal blood (non-invasive prenatal testing – NIPT) and subsequent molecular tests. The determinant of gender in humans is the sperm that fertilizes the egg cell. Depending on whether it has a 23, X or 23, Y karyotype, the gender of the fetus (46, XX or 46, XY) will be female or male, respectively. There are approximately 70 known genes responsible for sex differentiation in the human body. Their mutations can cause disorders of the process of differentiation of sexual characteristics. A flagship example is gonad dysgenesis syndrome (Swyer syndrome) [5], which consists of a function loss type mutation of the *SRY* gene, located on the Y chromosome, encoding a protein factor determining the development of the testicles. The above mutation results in the occurrence of a female phenotype in the individual with 46, XY karyotype.

Phenotypic sex characteristics in prenatal examination

Up to the 8th week of fetal life, the male and female genital organs are the same, and even during autopsy they cannot be distinguished. Between the 8th and 10th week of pregnancy, the production of testosterone, which initiates the differentiation of the penis and scrotum, begins. Between the 14th and 16th week of pregnancy, the development of the male genital organs begins – the penis with the urethra begins to be visible. After the 20th week, the testicles begin to descend into the scrotum, and in 93% of fetuses this process ends after the 30th week of pregnancy.

The second X chromosome, on which there is no SRY gene, and thus no testosterone is secreted, is involved in the development of the female genital organs. Between the 14th and 16th week of pregnancy, the clitoris is the same size as the penis (and therefore it is not recommended that the sex of the fetus be assessed at that stage of development). The labia are another structure visible during ultrasound examinations, testifying to the female sex. In addition, two X chromosomes are necessary for the appropriate differentiation of the ovaries and sex cells.

During prenatal diagnostic tests, there is a risk of a mistake and false recognition of the male sex in a female fetus. The abdominal attachment of the umbilical cord can be mistakenly considered as a penis. However, such an error is relatively rare and most often results from attempts to determine the sex of the fetus being made too early, especially in obese women. According to a 1985 study [6], erroneous gender identification accounted for less than 3% of cases, and all of these mistakes occurred before the 24th week of pregnancy. According to the same study, sex imaging was possible in 60% of cases at 18 weeks of gestation, and in 100% after the 20th week.

In the following decades there was development in both ultrasound scanners and the skills of the staff performing the scans. Hence, the correct recognition of fetal sex has become possible at increasingly earlier stages of pregnancy. As follows from the study by Gharekhanloo [7] of 2018, the percentage of correct sex determinations in fetuses during ultrasound examinations at the 11th and 12th weeks of pregnancy reached 91%. That was a significantly higher percentage of correctly diagnosed fetal sex compared to similar studies conducted in earlier years.

The breech position of the fetus is also a very important fetal factor, which can prove difficult in sex determinations for many, even experienced, ultrasound specialists, regardless of the gestational age. Such a position at the later stages of pregnancy can cause the fetus to effectively cover the perineal area with the limbs, which makes it impossible to assess its sex. The position that the fetus takes is very important at every stage of pregnancy and often affects the achievement of diagnostic success during prenatal tests [8].

Depending on the duration of pregnancy, the following characteristics can be observed in a healthy, well-developing fetus:

- in the 1st trimester of pregnancy – whether it is a boy or a girl, but always taking into account the risk of misinterpretation of the image,
- in the 2nd trimester of pregnancy – the penis and the scrotum (but without testicles in the scrotal sac) should be visible in boys,
- in the 3rd trimester of pregnancy – the penis, scrotum, and both testicles should be visible in boys (from 28th week of pregnancy).

What can interfere with the proper development of fetal sex?

Endocrine disorders in the fetus can cause disturbances of the process of proper differentiation of external sexual characteristics. Elevated levels of androgens in female fetuses can cause enlargement of the clitoris, adhesion of the labia, or lead to the development of a persistent genitourinary sinus. On the other hand, a reduced level of androgens in male fetuses may lead to underdevelopment of the penis (microphallus), hypospadias (as a result of incomplete connection of the urethra with the penis), cryptorchidism, bipartite scrotum, or the presence of a vaginal pouch. The development of sexual characteristics in the fetus, and thus their visibility in ultrasound examination, may be affected by the maternal use of hormonal drugs in the first trimester of pregnancy: progesterone (to maintain an endangered pregnancy) and androgens (for treatment of endometriosis). Some maternal conditions, such as acne, hirsutism, and infertility, are associated with higher androgen concentrations [9-12].

What ultrasound abnormalities can we observe in the course of prenatal examination of the fetus?

- Ambiguous fetal gender image (hermaphroditism) – the sex of the fetus visible, but unequivocal interpretation is difficult.
- Scrotal hernia and scrotal oedema.
- Hypospadias.
- Microphallus.
- Undescended testicles (> 30 weeks).
- Cloacal anomalies.

If any of the aforementioned irregularities are observed, the following questions should be answered:

- *Is it an isolated defect?*
- *Can it indicate a monogenic defect?*
- *Are there any other features that indicate a chromosomal defect?*
- *Should a congenital malformation syndrome be suspected?*

Hermaphroditism

There are special situations in which we see the genitals of the fetus but, despite this, the determination of sex is difficult. A hermaphrodite is an individual in whom ultrasound male and female sexual characteristics can be observed – the outlines of both the testicles and the ovaries are noticeable. Female pseudohermaphroditism is a situation when there is a masculinization of a female genetic individual (46, XX), because of the influence of androgen stimulation *in utero*. Such an exposure may occur in the course of congenital hypertrophy of the adrenal cortex, when a pregnant woman is taking exogenous androgens or when she has a virilizing tumour.

An analogous example is male pseudohermaphroditism in an individual with a male karyotype (46, XY), in which the features of insufficient masculinization with phenotypically visible features of testicular tissue are noticeable. This may be a consequence of insufficient testosterone synthesis or defects in testosterone receptor proteins [13, 14].

Scrotal oedema and scrotal hernia

One of the most common abnormalities that we observe in prenatal ultrasound is the occurrence of swelling around the testicles (Figure 3). A black, crescent-shaped lesion is then visible in the scrotum, which sometimes, as systemic abnormalities increase, occupies a large volume. Such a finding requires an increase in the diagnostic vigilance of the ultrasound specialist to be able to answer the question: is the swelling a result

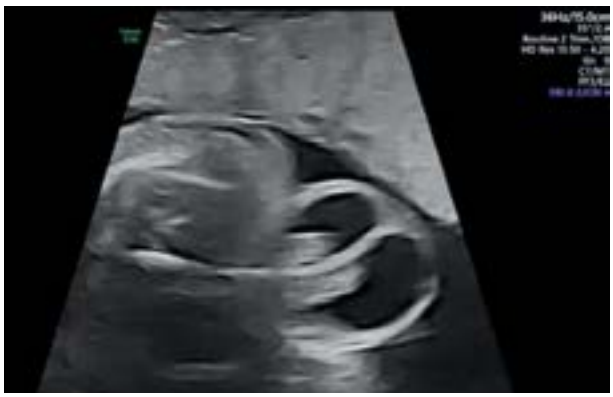

Figure 3. Massive swelling of the scrotum

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

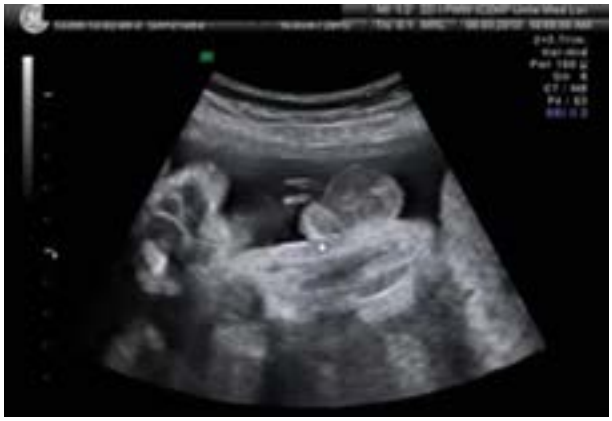

Figure 4. Hypospadias – 2D visualization of fetal examination at 30 weeks of pregnancy

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

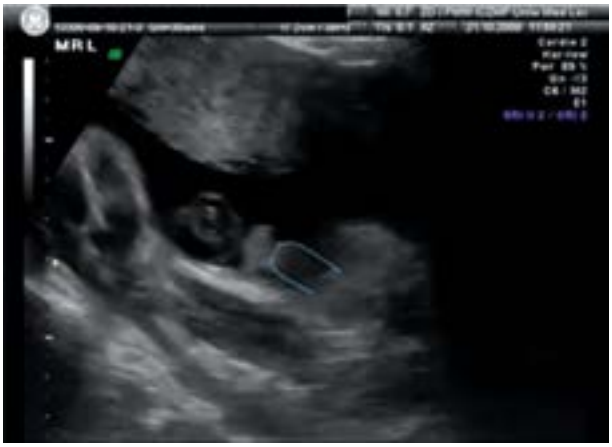

Figure 5. Hypospadias - 2D visualization of fetal examination at 30 weeks of pregnancy

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

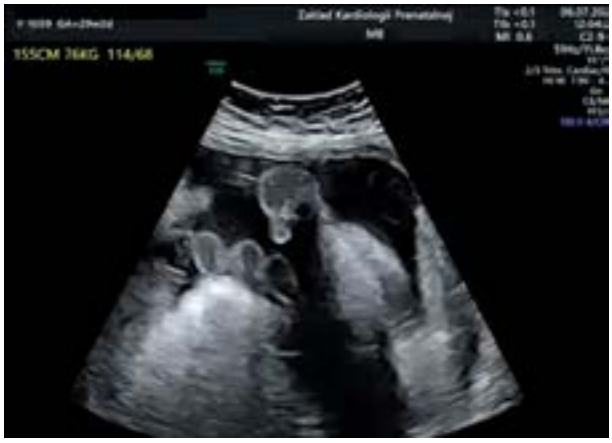

Figure 6. Hypospadias and cleft of foreskin – deletion of 18 p 11.32 and 21 p 11.1 (translocation 18/21)

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

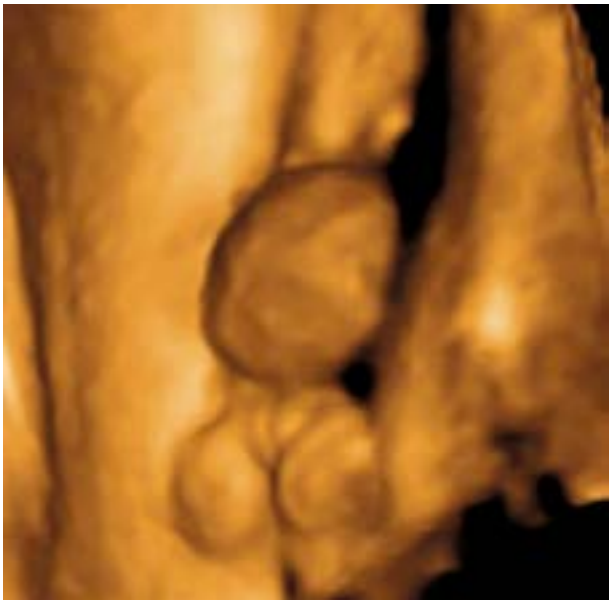

Figure 7. Exstrophy of the urinary bladder in 3D ultrasound

Source: Archives of the Department of Prenatal Cardiology, Polish Mother Memorial Research Institute in Lodz.

of cardiovascular failure, or is it a consequence of intrauterine infection in the fetus? Other features assessed during the examination, such as: the appearance and thickness of the placenta, the shape and size of the heart, the contractility of the ventricular muscle, the occurrence of atrioventricular regurgitation, the occurrence of anatomical defects of the heart, intestinal echogenicity, the size of the thymus gland, as well as the medical and epidemiological history of the pregnant woman, can be helpful in answering this question [15].

Hypospadias

A valuable diagnostic tip during difficult diagnostic cases of fetal sex determination is 3D imaging of the perineal area. During such visualization, it is possible to assess the distance between the anus and the genitals, which is shorter in boys. This marker is particularly useful in fetuses with microphallus observed in a 2D study [16]. Short and insufficiently developed, curved, or poorly visible in ultrasound examination penis and glans (an image of the so-called "hooded" prepuce) may suggest hypospadias (Figure 4-6). In order to diagnose hypospadias, it is also worth using 3D imaging, which improves the sensitivity and specificity of the examination. The advantage of the combination of 2D + 3D imaging in the diagnosis of hypospadias was confirmed in 2019 by Li et al. in "Scientific Reports" [17].

Other congenital urinary tract abnormalities

In addition to malformations of the genital organs, anomalies of the urinary system can be observed during ultrasound examination of the perineal area in fetuses. One such case was described by Łosińska in 2018 in Prenatal Cardiology. Urinary bladder exstrophy (Figure 7) was visible in the form of a large tumour that caused bulging of the skin integuments above the labia of the fetus [18]. Other congenital defects that are described during prenatal examination include the

co-occurrence of congenital megalourethra with congenital imperforate anus [19].

Summary

Prenatal diagnostics is always more difficult than postnatal diagnostics. Any abnormality found during prenatal examinations should increase the diagnostic vigilance of the examiner. The perceived anomaly can be isolated or may herald subsequent ones that may manifest themselves during that examination or a few weeks later. Some anomalies will be a part of well-known genetic syndromes (relatively rarely) or may (relatively often) constitute an uncharacteristic set of anomalies.

In the case of finding non-cardiac defects in the fetus, including the discussed topic "fetal sex visible but difficult to interpret unambiguously", the echocardiographic diagnosis: Normal Heart Anatomy and Normal Heart Study is a favourable prognostic factor.

The birth of a newborn in the case when the fetal gender is doubtful and difficult to name should take place in a referral centre where comprehensive medical assessment by qualified medical personnel (specialists in the field of clinical genetics, paediatric endocrinology, paediatric urology) is possible in a short time. Laboratory tests will include, among others, genetic reassessment, hormone concentrations, metal ion concentrations, and 24-hour urine collection. In such difficult cases, the final determination of the neonate's sex in the medical records should be postponed until the diagnostic process is completed. Correct early diagnosis is a chance for optimal growth, as well as the highest possible quality of life at the subsequent stages of development.

Conclusions

Fetal gender should be assessed by prenatal ultrasound and echocardiographic examination at the reference centre.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Maaji SM, Ekele BA, Bello SO, Morhason-Bello IO. Do women want disclosure of fetal gender during prenatal ultrasound scan? Ann Afr Med 2010; 9: 11-14.
2. Ralph K, Polson D. A woman's decision to know the sex of her child prior to birth. Ultrasound 2012; 20: 161-164.
3. Larsson M, Berglund M, Jarl E, Tydén T. Do pregnant women want to know the sex of the expected child at routine ultrasound and are they interested in sex selection? Ups J Med Sci 2017; 122: 254-259.
4. Størup G, Andreasen R, Andresen L, Boysen JN, Edvardsen G, Farlie R et al. Kønsbestemmelse af fostre ved ultralyd dfms.dk. 2015: 1-25. www.dfms.dk/images/Guidelines/Koensbestemmelse_af_fostre_ved_ultralydsscanning_Final_version_23-1-2015 _ 15-9-2015.pdf.
5. Mohnach L, Fechner PY, Keegan CE. Nonsyndromic disorders of testicular development. 2008 May 21 [updated 2016 Jun 2]. In: Adam MP, Ardinger HH, Pagon RA et al. (eds.). GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
6. Hobbins JC. Determination of fetal sex in early pregnancy. N Engl J Med 1983; 309: 979-980.
7. Gharekhanloo F. The ultrasound identification of fetal gender at the gestational age of 11-12 weeks. J Family Med Prim Care 2018; 7: 210-212.
8. Karuga FF, Szmyd B, Respondek-Liberska M. Fetal congenital heart disease and fetal position – are they related? Prenat Cardio 2019; 1: 33-36.
9. Karrer-Voegeli S, Rey F, Reymond MJ, Meuwly JY, Gaillard RC, Gomez F. Androgen dependence of hirsutism, acne, and alopecia in women: retrospective analysis of 228 patients investigated for hyperandrogenism. Medicine (Baltimore) 2009; 88: 32-45.
10. Barrett ES, Swan SH. Stress and androgen activity during fetal development. Endocrinology 2015; 156: 3435-3441.
11. Mandell J, Bromley B, Peters CA, Benacerraf BR. Prenatal sonographic detection of genital malformations. J Urol 1995; 153: 1994-1996.
12. Pang S. Congenital adrenal hyperplasia. Baillieres Clin Obstet Gynaecol 1997; 11: 281-306.
13. De Castro M, Elias LL. Causas raras de pseudo-hermafroditismo feminino: quando suspeitar? [Rare forms of female pseudohermaphroditism: when to investigate?]. Arq Bras Endocrinol Metabol 2005; 49: 126-137.
14. Celminson R, Medina Doménech R. Mujer u hombre? Hermafroditismo, tecnologías médicas e identificación del sexo en España, 1860-1925 [Woman or man? Hermaphroditism, medical technologies and sex identification in Spain, 1860-1925]. Dynamis 2004; 24: 53-91.
15. Vökt CA, Visca E, Tercanli S. Sonographische Befunde bei materno-fetalen Infektionen [Ultrasound findings in fetal infection]. Ther Umsch 2008; 65: 667-674.
16. Natsuyama E. Sonographic determination of fetal sex from twelve weeks of gestation. Am J Obstet Gynecol 1984; 149: 748-757.
17. Li X, Liu A, Zhang Z, An X, Wang S. Prenatal diagnosis of hypospadias with 2-dimensional and 3-dimensional ultrasonography. Sci Rep 2019; 9: 8662.
18. Łosińska J, Respondek-Liberska M. Extraordinary bulging mass in the foetus – a case report of bladder exstrophy. Prenat Cardio 2018; 1: 48-52.
19. Chao AS, Chang YL, Hsieh PC. Prenatal diagnosis of congenital megalourethra with imperforate anus. BMC Pediatr 2019; 19: 123.

Division of work:
Kacper Deska (ORCID: 0000-0002-5416-5711): research concept and design, collection and/or assembly of data, writing the article
Iwona Strzelecka (ORCID: 0000-0003-3469-7064): research concept and design, collection and/or assembly of data, writing the article, critical revision of the article
Julia Murlewska (ORCID: 0000-0002-8266-4585): research concept and design, collection and/or assembly of data
Krzysztof Preis (ORCID: 0000-0002-8097-3552): research concept and design, collection and/or assembly of data, data analysis and interpretation, critical revision of the article
Maria Respondek-Liberska (ORCID: 0000-0003-0238-2172): research concept and design, collection and/or assembly of data, data analysis and interpretation, writing the article, critical revision of the article