PROFESSIONAL PROFILE

1. **Name and surname: Marcin Wiecheć.**
2. **Diplomas, scientific degrees - with the name, place and year of obtaining and the title of doctoral dissertation:**

1998 - graduate in medicine, Faculty of Medicine Jagiellonian University in Kraków;
2004 - certificate of skills in obstetrics, gynaecology and prenatal diagnosis, the Polish Society of Ultrasonography;
2007 - completed medical specialization in obstetrics and gynaecology with very good grade - Medical Examination Centre in Łódź;
2009 - certificate of competence in invasive procedures during pregnancy, Foetal Medicine Foundation, UK;
2015 - doctor of medical sciences based on the thesis: "The role of ultrasonography in detecting functional disorders of the cardiovascular system in the foetus and congenital heart defects in the late first trimester of pregnancy", Faculty of Medicine at the Jagiellonian University, *dissertation with honours*.

3. Information on current employment in scientific units:

- 2000-2007 - junior assistant in the Complex of Gynaecology and Obstetrics Departments at the University Hospital in Kraków (2000-2004 Gynaecology and Obstetrics Department; 2004-2006 Department of Gynaecology and Infertility, 2006-2007 Department of Gynaecology and Oncology);
- 2007 - senior assistant in the Department of Clinical Gynaecology and Oncology at the University Hospital in Krakow;
- 2008 - 2009 - specialist registrar at the Centre for Foetal Care, Imperial College Healthcare, Queen Charlote's and Chelsea Hospital, London, United Kingdom;
- 2009 - until now - senior assistant in the Complex of Gynaecology and Obstetrics Departments at the University Hospital in Kraków (Department of Obstetrics and Perinatology);
- 2012 - until now - assistant in the Gynaecology and Obstetrics Chair - Gynaecology and Oncology Department, the Medical Faculty of the Jagiellonian University Medical College in Kraków.

4. Achievements indicated* under Art. 16 paragraph 2 of the Act of 14 March 2003 on Academic Degrees and Scientific Title and Degrees and Title in Art (Journal of Laws No. 65, item 595 as amended).

a) title of the scientific/artistic achievement:

One-theme series of publications:
"The analysis of the effectiveness of screening for trisomy 21, trisomy 18 and monosomy X in the foetus by ultrasound in the late first trimester of pregnancy without additional determination of serous biomarkers."

It is a series of 5 publications which is an individual contribution to science and the development of knowledge on the use of modern ultrasound in detecting the most common trisomy and monosomy X in the foetus.

These publications have been published in reputable, peer-reviewed journals positioned in the Journal Citation Reports (JSC) database in the field of gynaecology and obstetrics based on the number of citations:

- ***Fetal Diagnosis and Therapy, Karger AG, Basel, Switzerland***;
- ***Journal of Maternal-Foetal and Neonatal Medicine, Taylor & Francis Group, United Kingdom*** - the official journal of the European Association of Perinatal Medicine; the International Society of Perinatal Obstetricians; and the Federation of Asia and Oceania Perinatal Societies;
- ***Journal of Perinatal Medicine, De Gruyter, Germany*** - a magazine associated with the World Association of Perinatal Medicine.

The achievement has been documented in the cycle of 5 original works.
The total IF for these publications is **9.53 [KBN/MNiSW (Committee for Scientific Research/Ministry of Science and Higher Education) - 115 pts.]**. These works were published after obtaining the degree of doctor of medical sciences.

b) (Author / authors, title / title, year of publication, publisher):

Paper 1
Wiechec M, Knafel A, Nocun A, Matyszkiewicz A, Juszczak M, Wiercinska E, Latała E. How Effective Is First-Trimester Screening for Trisomy 21 Based on Ultrasound Only? Fetal Diagn Ther. 2016; 39:105-12.
IF – 2,59; KBN/MNiSW – 25 pts. *(original paper)*

*My contribution to the work consisted of: the conception and study design, data collection, analysis and interpretation of results, statistical analysis, ensuring the integrity of the study, literature review, intellectual content of the manuscript, editing the manuscript, correction and final approval of the version to be published. I estimate my proportionate contribution to the implementation of the work at **70%.***

Paper 2
Wiechec M, Nocun A, Knafel A, Wiercinska E, Sonek J, Rozmus-Warcholinska W, Orzechowski M, Stettner D, Plevak P. Combined screening test for trisomy 21 - is it as efficient as we believe? J Perinat Med. 2016 Mar 23. pii: /j/jpme.ahead-of-print/jpm-2016-0031/jpm-2016-0031.xml. DOI: 10.1515/jpm-2016-0031.
IF – 1.79; KBN/MNiSW – 25 pts. *(original paper)*

*My contribution to the work consisted of: the conception and study design, data collection, analysis and interpretation of results, statistical analysis, ensuring the integrity of the study, literature review, intellectual content of the manuscript, editing the manuscript, correction and final approval of the version to be published. I estimate my proportionate contribution to the implementation of the work at **60%.***

Paper 3
Wiechec M, Knafel A, Nocun A, Matyszkiewicz A, Wiercinska E, Latała E. How effective is ultrasound-based screening for trisomy 18 without the addition of biochemistry at the time of late first trimester? J Perinat Med. 2016; 44:149-59.
IF – 1,79; KBN/MNiSW – 25 pts. *(original paper)*

*My contribution to the work consisted of: the conception and study design, data collection, analysis and interpretation of results, statistical analysis, ensuring the integrity of the study, literature review, intellectual content of the manuscript, editing the manuscript, correction and final approval of the version to be published. I estimate my proportionate contribution to the implementation of the work at **70%.***

Paper 4
Wiechec M, Knafel A, Nocun A, Ludwin A; Ludwin I, Maczka M, Zietek D, Pasternok M, Moosburger D, Zalewski S, Rozmus-Warcholinska W (2016). Screening for trisomy 18 using traditional combined screening vs. ultrasound-based protocol in tertiary centre environment. The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2016.1224837
IF – 1,67; KBN/MNiSW – 20 pts. *(original paper)*

*My contribution to the work consisted of: the conception and study design, data collection, analysis and interpretation of results, statistical analysis, ensuring the integrity of the study, literature review, intellectual content of the manuscript, editing the manuscript, correction and final approval of the version to be published. I estimate my proportionate contribution to the implementation of the work at **60%.***

Paper 5
Wiechec M, Knafel A, Nocun A, Wiercinska E, Ludwin A, Ludwin I (2016): What are the most common first trimester ultrasound findings in cases of Turner Syndrome? The Journal of Maternal-Fetal & Neonatal Medicine, DOI:10.1080/14767058.2016.1220525.
IF – 1,67; KBN/MNiSW – 20 pts. *(original paper)*

*My contribution to the work consisted of: the conception and study design, data collection, analysis and interpretation of results, statistical analysis, ensuring the integrity of the study, literature review, intellectual content of the manuscript, editing the manuscript, correction and final approval of the version to be published. I estimate my proportionate contribution to the implementation of the work at **70%.***

Attached:
- Copies of the works (Annex 3)
- Statement of co-authors about the individual contribution of copyright (Annex 4)
- IF confirmation certified by the Library of Science, Polish Mother's Memorial Hospital Research Institute (Appendix 7)

c) discussion on the scientific/artistic objective of the above work/works along with the results achieved and discussion on the possible use:

Introduction:

According to the Eurostat report of 2015, the average age of women giving birth to their first child in the European countries is 29 years. Currently, more than 40% of the citizens of the European Union become mothers for the first time after thirty years of age. This noticeable tendency to delay gestational age gradually increases the incidence of trisomy 21 by 0.9% per year. In recent years, it accounted for 11.8 per 10 000 births (Shin et al., 2009). A similar trend was noted on the incidence of trisomy 18 showing a ratio of 3.95

per 10 000 births in 1995-1999 and reaching 6.94 per 10 000 births in registers from the years 2005-2009 (Nicolaides, 2011). However, we do not observe the influence of gestational age on the incidence of monosomy X which accounts for 1 per 2500 female births. Nevertheless, this is one of the most common human chromosomal aberrations observed in 1-2% after fertilization (Barr et al., 2002).

Combined Screening Test (CST) became the gold standard of screening for both primary trisomy and monosomy X in pregnant women. It was developed in the early twenty-first century and is based on the adjustment of the basic risk of having a child with trisomy, which results from the maternal age. The test uses the ultrasound measurement of the fluid layer thickness on the neck of the foetus between weeks 10 and 15 of pregnancy called Nuchal Translucency (NT) and serum levels of two biomarkers: free β-Human Chorion Gonadotropin (fβ-hCG) and Pregnancy-Associated Plasma Protein A (PAPP-A). Nuchal Translucency is considered a primary ultrasound marker of chromosome aberration. The final CST result is the value of individual risk for the most common trisomy, which qualifies pregnant for further proceedings. Numerous algorithms of this test were developed, but the algorithm created by the Foetal Medicine Foundation (FMF) (Snijders et al., 1996; Luthgens, 2008) is the most widely used in the world. According to the authors of this method and others who cooperate with the FMF, the Detection Rate (DR) of this procedure for the detection of trisomy 21 reaches approx. 90% at the False Positive Rate (FPR) of 2-3% (Spencer 2003, Nicolaides 2005, Kagan 2008). A group of scientists, who worked independently from the FMF, did not receive such good results, obtaining DR of 80% at FPR of 5-10% (Wapner, 2005; Norton 2015). Further research in this field aimed at optimizing the CST effectiveness by adding secondary correction ultrasound parameters known as markers of the foetus, such as the evaluation of ossification of the nose, the activity of the tricuspid valve or the flow spectrum through the ductus venosus, which allow for the FPR reduction (Nicolaides et al. 2011; Ghaffari et al. 2012; Karadzov-Orlic et al. 2012). These parameters show high specificity for the most common trisomies and monosomy X in the foetus. In contrast, serum biomarkers are only non-specific to the dysfunction of the placenta. It was recognized, however, that secondary ultrasound parameters are more difficult to the widespread application because of the learning curve and the need to use programs, which verify the correctness of their application (Senate et al., 2003; Falcon et al. 2006; Maiz et al. 2008). Additionally, works were carried out on the revision of the classic screening strategy based on a rigid cut-off value and the consequent distribution of the results into those indicating low or elevated risk of having a child with trisomy with the simultaneous indication for a diagnostic test. The method of step-wise screening was tested in this respect, an example of which is the Integrated Test (IT) comprising second trimester of pregnancy biomarkers (Currier et al. 2012). A delay in obtaining a screening result using this strategy almost to a half of pregnancy disqualified the method from the widespread use. On the other hand, it was proven that the strategy of contingent screening was the most optimal from the point of view of statistical significance. The method uses three ranges of simple CST results: low, intermediate and increased risk. In this strategy, patients with an intermediate CST risk are further assessed, for example by using secondary ultrasound parameters and based on the secondary risk correction are qualified to the group of low- or high-risk (Nicolaides et al., 2005; Cuckle et al. 2008). Non-Invasive Prenatal Testing (NIPT), which was introduced in recent years, has high sensitivity and is based on sequencing the free DNA of the foetal chorionic origin taken from serum of the pregnant. The test is being increasingly used as a method of verifying the results of intermediate risk in the strategy of conditional screening instead of secondary ultrasound parameters (Gyselaers et al., 2015). However, because of the high cost, NIPT tests have not so far replaced in any country traditional screening strategy based on CST (Neyt et al. 2014). They show sensitivity for trisomy 21 of 99% at FPR below 1%, but they have limitations when the chorionic mass is small, which is

manifested by the low PAPP-A levels. This situation often occurs, for example in trisomy 18 of the foetus, which may be translated into failure of this method in as many as 8% of determinations. NIPT is also less sensitive in terms of sex chromosome aberrations, at 88% for monosomy X with 0.12% FPR (Gil et al. 2014). In recent years, we encounter alarming rates of false-positive CST results in pregnant women after 40 years of age. Some authors have opted for the elimination of the maternal age factor in this group proposing the so-called concept of absolute risk (Wapner et al., 2003; Gebbe et al., 2019; Schmidt et al., 2010; Engels et al. 2013).

In Poland screening conditions for chromosomal aberrations in the foetus are unusual in relation to Western Europe. This is due to the fact that the National Health Fund refunds screening only in patients who meet one of the following criteria: over 35 years of age (a woman shall have the test in the calendar year in which she reaches 35 years), a previous pregnancy with chromosomal aberration of the foetus or child, structural chromosomal aberrations in the pregnant or the child's father, a much larger risk of having a child affected by one-gene or multi-factorial disease, abnormal ultrasound or biochemical tests found during pregnancy indicating an increased risk of chromosomal aberration or a defect of the foetus (http://www.nfz-krakow.pl). At the same time, according to the statistical yearbook of the 2012, the average maternal age in our country is 29 years. In view of this,
a large group of pregnant women do not meet the requirements for screening refund, including women who often forgo the evaluation of biomarkers for economic reasons and subject only to the screening based only on ultrasound parameters. Another equally important reason which distinguishes Polish screening conditions is bad experience of Polish gynaecologists and patients with serum biomarker analysers, which were not accredited by the FMF and as such show high rates of false-positive results leading to an excess of unnecessary diagnostic tests, which are always a potential threat to the maintenance of pregnancy. Apart from factors, such as increased BMI, smoking, diabetes, renal failure, or assisted reproductive techniques, whose negative impact on the effectiveness of biomarkers in CST was well-described in the literature, there are certainly unexplored modulating factors (Gierris et al. 2009; Spencer, 2014; Valentin et al., 2015). We cannot exclude the impact of gestagens on the serum levels of biomarkers. Unlike in Western Europe, they are widely used in Poland in the pathology of early pregnancy. Also, the influence of thyroid disorders in pregnancy, which are increasingly observed in our country, is unknown. These factors favoured the high level of ultrasound competence among Polish doctors who carry out screening and focus their attention on this element of the Combined Screening Test. According to data from the FMF, starting from December 2015, 94% of the doctors successfully passed audit in the assessment of ossification of the nose, 65% in the tricuspid valve activity and 73% in the flow spectrum though the ductus venosus. For comparison, at the same time in the UK, which is the home of aneuploidy screening in the foetus, only 77% of active examiners confirmed their competence in the assessment of nose ossification, 37% in the evaluation of the tricuspid activity and 35% of the ductus venosus flow.

Given the above facts and taking advantage of the unique Polish screening conditions, as the first in the world I decided to analyse the effectiveness of multi-parameter ultrasound in the late first trimester as self-screening test for detection of trisomy 21, trisomy 18 and monosomy X in the foetus. So far, no group of authors has decided to undertake this issue without serum biomarkers. Another objective of my study was to determine the most common combination patterns of suspected ultrasound parameters in foetuses with trisomy 21, trisomy 18 and monosomy X compared to the foetuses without chromosomal aberrations. As the specific FMF algorithm for the detection of trisomy 21 and trisomy 18 is available, I conducted the first Polish two-arm study comparing the classic CST with the proposed method based on independent multi-parameter ultrasound. Taking into account the fact that

some authors question the maternal age factor in patients over 40, I have also made the detailed evaluation of screening effectiveness by age groups.

Publication No. 1

Wiechec M, Knafel A, Nocun A, Matyszkiewicz A, Juszczak M, Wiercinska E, Latała E. How Effective Is First-Trimester Screening for Trisomy 21 Based on Ultrasound Only? Fetal Diagn Ther. 2016; 39:105-12. DOI: 10.1159/000434632.
IF – 2,59; KBN/MNiSW – 25 pts.

Objectives of the **Publication No. 1** published in Foetal Diagnosis and Therapy (Karger AG, Switzerland) were as follows:

1. The analysis of aneuploidy positive markers and structural abnormalities in foetuses with trisomy 21 compared to foetuses without chromosomal aberrations;
2. The evaluation of the screening effectiveness of the multi-parameter ultrasound juxtaposed with maternal age and the test of reference based on NT and maternal age;
3. The assessment of the screening effectiveness of the tests from point 2 in age groups 26 to 30 years, 31-35 years, 36-40 years and over 40 years of age

A prospective analysis based on 6265 ultrasound examinations performed only by three examiners was the primary and original element of the methodology of this study. Two examiners had very high diagnostic competence (over 8 years of the effective audit within the whole panel of sonographic aneuploidy markers). The study group comprised 84 foetuses with trisomy 21. The study used a standardized protocol, including aneuploidy markers (NT, ossification of the nose, the tricuspid valve function, the assessment of the flow spectrum through the ductus venosus, a number of umbilical cord vessels); the assessment for structural defects with established risk of aneuploidy (atrio-ventricular septal defect, holoprosencephaly, giant bladder, diaphragmatic hernia and umbilical/umbilical cord hernia); and major structural defects without the effect on the aneuploidy risk algorithm created by FMF (limb defects, acrania, encephalocele, cleft palate, single heart chamber, the image suspected of the arterial cone defect at the level of projection of three blood vessels with the trachea, cysts of the abdominal cavity, expansion of the neck lymphatic pockets). An important element of the methodology of this study was the FMF risk assessment algorithm without biomarkers, which was applied for the first time in literature. In this publication, I have based on high percentage rates of positive aneuploidy markers, which were reported in the literature in foetuses with trisomy 21. They included increased Nuchal Translucency (observed in 76% of cases by Snijders et al., 1996), delayed ossification of the nose (in 68.8% of cases by Cicero 2004), tricuspid regurgitation (in 65.1% of cases by Faiola et al. 2005), and the abnormal flow profile through the ductus venosus (in 73.3% of cases by Huggon et al., 2004). Therefore, I used the multi-parameter test covering all aneuploidy markers, the foetal heart rate and maternal age (NT+ test), and the reference test based on NT, heart rate and maternal age (test NT).

In the **Publication 1** I have shown that 71.4% of foetuses with trisomy 21 presented positive aneuploidy markers in coincidences. The most common combination was thickened nuchal translucency and tricuspid insufficiency (63.5%); the second most common was thickened Nuchal Translucency and weakened ossification of the nose (28.6%). In turn, the coincidence of positive aneuploidy markers was shown in only 1.1% of the study group of foetuses with euploidy. Isolated aneuploidy markers occurred in 28.6% of foetuses with trisomy 21, including 19% with isolated thickened nuchal translucency. In the group of foetuses with euploidy, 7.7% had isolated markers, including thickened Nuchal Translucency in 3.2%. So far, no group of researchers has published the analysis of coincidence of positive aneuploidy markers in trisomy 21 without the levels of biomarkers.

As for non-cardiac structural abnormalities, foetuses with trisomy 21 showed 5.3 times more anomalies, mainly oedema. I have shown heart defects were 35.8 times more likely in trisomy 21 compared to euploidy. Leakage defects dominated in this group of anomalies. The analysis of screening effectiveness for multi-parameter NT+ test using the ROC (Receiver Operating Characteristic) method showed sensitivity of 91.7% at the FPR rate 3% and of 95.2% at the FPR 5%. I used this method to determine the risk cut-off value of 1/100.

The study showed the correlation between the NT+ test screening effectiveness and the maternal age. As for sensitivity, I have demonstrated an upward trend from the value of 94.7% for the age group 26-30 years to 100% for pregnant women over 41 years of age with a decrease in sensitivity to 83.9% in the group of 31-35 years, which was difficult to explain. The false positive rate increases with age, ranging from 1.6% for women aged 26-30 years to 12.9% for those over 41 years of age.

Conclusions from the Publication No. 1:

1. In view of the reported common coincidences of positive sonographic aneuploidy markers in Down syndrome, the ultrasound multi-parameter assessment of the foetus is important to the detection of trisomy 21.
2. The early assessment of the heart based on the ultrasound without biomarkers is essential in the detection of trisomy 21.
3. The multi-parameter ultrasound test NT + shows screening effectiveness comparable to the CST level with secondary ultrasound aneuploidy markers. It may therefore be an effective alternative to the CST test for the detection of trisomy 21.

The practical and scientific importance of the Publication 1 results:
The results of this work are essential to prenatal diagnosis centres, particularly in the trisomy 21 screening in patients at risk of false-positive CST results as a consequence of the biochemical component. In this group, we should distinguish patients with diabetes, kidney disease, treated with assisted reproductive techniques, as well as those with multiple pregnancies. In such cases, we can use NT+ test described in this paper. In the Publication 1, I also paid attention to the differences resulting from screening effectiveness using NT+ test depending on the maternal age, especially in women over 40 years of age.

Publication No. 2

The results of Publications 1 and numerous cases of false positive CST results observed in my daily work showing an increased risk for trisomy 21 only due to abnormal levels of biomarkers, prompted me to design a two-arm prospective study on screening for Down's syndrome. This is a subject of Publication 2 (Journal of Perinatal Medicine,
De Gruyter, Germany). The first arm of the study, which comprised 5733 pregnant women and 87 foetuses with trisomy 21, was based on the NT+ test results according to the methodology described above with the risk cut-off of 1/100 as in Publication 1. I called this arm the Ultrasound Screening Group. The second arm of the study, which was called Combined Screening Group (CSG), consisted of 5145 pregnant women and 51 foetuses with trisomy 21, and was based on the results of the traditional CST. The results were analysed using the cut-off risk values of 1/100 and 1/300. Both arms of the study did not statistically differ in terms of trisomy 21 prevalence. In both treatment arms, I additionally used the original method of absolute risk (AR), ignoring the aspect of maternal age with the cut-off of 1,2.

Objectives of the **Publication 2** were as follows:

1. A comparison of two methods of late first trimester screening for trisomy 21 detection: CST and NT+ tests, which I have introduced into the literature in the **Publication 1**;
2. The evaluation of the effect of maternal age on the screening methods used in the work.

According to the available knowledge this is the first study to compare these two methods of screening based on the total group of 10 878 pregnant women. In this group, I have shown 138 foetuses with trisomy 21. The two arms of the study pregnant women did not statistically differ in terms of BMI. As for the analysed foetuses, there was no significant difference in the average NT thickness or the crown-rump length (CRL). The tests used in the ultrasound arm (NT+ and AR NT+) showed higher specificity, positive predictive value and diagnostic accuracy as compared with the tests applied in the CSG arm (CST 1/100, CST 1/300 and AR CST). Based on the ROC evaluation NT+ test had sensitivity of 90% at FPR 3% and 94% at FPR 5%. The CST, in turn, had sensitivity of 78% at FPR 3% and 85% at FPR 5%.

Key findings of the Publication No 2:

1. NT + test is an effective alternative to the traditional CST for trisomy 21 screening;
2. In the population studied by the author and co-workers, CST shows a much higher rate of false-positive results compared to literature data. This may result from the lower PAPP-A serum levels in analysed pregnant women and a relatively high proportion of foetuses showing the thickened NT in both arms;
3. The method of the absolute risk effectively reduces the number of false positive results in NT + test and CST in the group of pregnant women over 41 years of age.

The practical and scientific importance of the Publication No. 2:

The study results are a strong argument to re-discuss the CST effectiveness, especially in terms of false-positive results. This is of great importance for the Polish population exhibiting suboptimal effectiveness of this method. Perhaps, other populations also show a similar profile of biomarkers, which disturbs screening effectiveness. Describing in the introduction the Polish conditions of screening I have mentioned that until this publication gynaecologists and clinical geneticists used in their everyday work the results of screening without biochemistry, which did not allow for the interpretation of sensitivity, false-positive results and the impact of maternal age on trisomy 21 screening effectiveness. Like in the works of other authors, I have shown in this publication difficult to accept false positive results exceeding 40% in CST for pregnant women over the age of 40. In this group, I have effectively reduced this value using the absolute risk method without adversely affecting the sensitivity of trisomy 21 detection. This strategy is of great practical importance because it allows for significant reduction of the number of unnecessary diagnostic tests in this age group. Currently, the strategy of conditional screening using the CST as an initial method supplemented with high sensitivity NIPT tests is being discussed in the literature. In my assessment, the NT+ test would have at this point a more appropriate preliminary role due to the greater specificity and independence from biomarkers, which are influenced by a number of factors in the body of the pregnant.

Publication No. 3

Taking into account the gradually increasing incidence of trisomy 18, a high percentage of potential determination errors in high sensitivity NIPT tests for this aneuploidy and the absence of clear screening guidelines for Edwards' syndrome in the foetus and the

experience gained in **Publications 1 and 2**, I have designed the methodology for the **Publication 3**, which has been published in the Journal of Perinatal Medicine, De Gruyter, Germany. Unlike Down's syndrome, which was the core of the above-mentioned works,
I assumed bigger effectiveness of multiparametric ultrasound in trisomy 18 due to a high incidence of structural abnormalities in foetuses with this chromosomal aberration. Here, the literature emphasizes the presence of umbilical/umbilical cord hernia (seen in 49% of the foetuses), abnormalities of the upper limbs (in 6%), giant bladder (in 4%), and heart defects (in 83-84%), based on the publications of Yeo et al. 2003, Yang et al. 2005 and Sepulveda et al. 2010. In addition, the foetuses with trisomy 18 demonstrate a large percentage of aneuploidy positive markers, such as nuchal translucency thickening (in 76% by Snijders et al., 1996 and in 91% by Sepulveda et al. 2010), delayed ossification of the nose (in 57.1% by Cicero et al. 2003), tricuspid regurgitation (in 53% by Faiola et al. 2005), the abnormal flow profile through the venosus line (in 37.9% by Huggon 2004) and two-vessel umbilical cord (in 77% by Rembouskos et al., 2003). Given the above, the methodology of the study I involved the early assessment of foetal anatomy with the evaluation of heart in terms of a number of inflows into the chambers, the proportion of the chamber sizes, large leakage in the septum and the abnormal image of the projection of the three vessels with the trachea.

The Publication 3 is the world's first examination of the effectiveness of trisomy 18 screening based on the algorithm specific for trisomy 18 and prepared by the FMF, but without using biomarkers. In view of the literature data on the use of the methodology combining the algorithms for trisomy 18 and trisomy 21 and in order to better detect Edwards' syndrome, I additionally used in the Publication 3 the analysis of the effectiveness of the assessment of an individual risk for trisomy 21 (Breathnach et al. 2007, Kagan et al. 2008).
Objectives of the **Publication 3** were as follows:

1. The analysis of positive aneuploidy markers and structural abnormalities in foetuses with trisomy 18 compared to foetuses without this chromosomal aberration;
2. The development of the logistic regression model based on the most frequent abnormal ultrasound images in trisomy 18;
3. The assessment of the effectiveness of trisomy 18 screening using trisomy 18 and trisomy 21 multi-parameter algorithms developed by FMF without serum biomarkers, but with particular emphasis on the early foetal anatomy ultrasound;
4. The analysis of the effect of maternal age on the screening effectiveness for trisomy 18 using the method described in paragraph 1.

The study population comprised 5650 pregnant women and included 37 cases of trisomy 18. As for basic parameters, no statistically significant differences were shown between the cases of euploidy and trisomy 18 in terms of maternal age, parietal-sitting length of the foetus and the heart rate. However, there were differences in terms of nuchal translucency thickness.

Just as in the **Publication 1**, which focused on trisomy 21, in **the Publication 3** I have presented an analysis of the coincidence for aneuploidy positive markers. Only 2.7% of the study trisomy 18 cases did not show any aneuploidy positive marker, which affected 91.1% of euploidy foetuses. Isolated positive ultrasound markers were present in only 5.4% of trisomy 18 cases and in 7.8% of euploidy foetuses. The most commonly observed coincidences of aneuploidy positive markers in the examined trisomy 18 foetuses were increased nuchal scan and tricuspid regurgitation (43.2%), and subsequently thickened nuchal scan with delayed ossification of the nose (40.7%). These combinations occurred in only 0.3% of euploidy foetuses. I have found non-cardiac anomalies in 35.1% of trisomy 18 cases compared to 0.8% of foetuses without this chromosomal aberration. As for congenital heart defects, the anomalies were confirmed in 70.3% of trisomy 18 foetuses as compared to only 0.5% of euploidy cases. The most common features of trisomy 18 shown in **the**

Publication 3 were subjected to the logistic regression model with the statistical significance for the following parameters: nuchal scan above percentile 95 (OR = 6), tricuspid regurgitation (OR = 63.6), two-vessel umbilical cord (OR = 23.9), dominance of the right heart (OR = 134.6) and umbilical hernia (OR = 50.7).

With the risk cut-off values of 1/100, the multi-parameter algorithm specific for trisomy 18 had sensitivity of 94.6% at FPR 1.1%. For comparison, literature data indicate that the simple CST supported by secondary ultrasound aneuploidy markers exhibits sensitivity between 79% and 93% at FPR 0.2-0.5 (Tul et al., 1999; Spencer et al., 2002; Breathnach 2007; Kagan et al. 2008). For comparison, the non-specific algorithm for trisomy 21 from the Publication 3 had sensitivity of 78.4% at FPR 3.3% for the trisomy 18 detection.

Examining the effect of maternal age on the effectiveness of trisomy 18 screening using the multi-parameter ultrasound, specifically for this aneuploidy, I have shown an upward trend for sensitivity from 90% for the age group of 26-30 years to 100% for pregnant women over 36 years of age with a decrease in sensitivity in the group 31-35 years to 85.7%. The false positive result rate increased with maternal age and ranged from 2% for women aged 26-30 years to 12.9% for pregnant women over 41 years of age.

Key findings of the Publication No. 3:

1. The study results demonstrate the importance of the multi-parameter foetal ultrasound assessment in the trisomy 18 detection due to the often coincidences of aneuploidy markers in chromosome aberrations.
2. The early anatomy evaluation with particular attention to the early examination of the heart greatly improves the trisomy 18 detection.
3. The multi-parameter algorithm developed by FMF for trisomy 18 without biomarkers and using the cut-off of 1/100 has higher detection sensitivity for Edwards' syndrome compared to the literature, at a slightly higher rate of false positive results of 1%.

The practical and scientific importance of the Publication No. 3:

This is the first work to confirm the high effectiveness of trisomy 18 screening using the independent multi-parameter ultrasound and the assessment of individual risk according to the algorithm FMF without the use of biomarkers. This method can be considered as an alternative to the CST. The results of this work are essential to prenatal diagnosis centres, particularly in the field of aneuploidy screening of patients with a potential risk of false positive CST results as a consequence of the biochemical component, such as diabetes, kidney disease, the use of assisted reproduction techniques, or multiple pregnancy. We should also take into account the importance of this work at this time of transformation of CST-based screening to the screening using NIPT in the first line. Because of the high proportion of cases with the low PAPP-A levels having the small weight of the placenta, trisomy 18 is at the risk of failure in NIPT determination of approx. 8% (Revello et al. 2016). The high specificity multi-parameter ultrasound does not have this drawback.

In the **Publication 3** I have also emphasized the difference resulting from the screening effectiveness using the described method depending on the maternal age, especially in women over 40 years of age.

<u>Publication No. 4</u>

On the basis of the results of **Publication 3**, which show the reliable effectiveness of ultrasound trisomy 18 screening and the two-arm study on trisomy 21 (**Publication 2**), I have developed the methodology which allows for a comparison of effectiveness of the commonly used screening CST for the trisomy 18 detection compared to the method described in the **Publication 3**. Given different cut-off values for screening assays used for trisomy 18

detection, which were reported in the literature, I additionally applied the most frequently observed cut-offs: 1/50, 1/100 and 1/300 (Spencer et al., 2003; Wojdemann et al., 2005; Koster et al . 2010; Breathnach et al. 2007).
In this work I have introduced the concept of a two-arm prospective study as in the Publication 2 on trisomy 21. **The Publication 4** has been described in The Journal of Maternal-Foetal & Neonatal Medicine, Taylor & Francis Group, UK.

The objectives of **the Publication 4** were as follows:

1. A comparison of two methods of late first trimester screening for trisomy 18 detection: CST and multi-parameter test based on the ultrasound parameters without biomarkers.
2. The evaluation of the effect of maternal age on the screening methods used in the work.

According to the literature, it is the first study to compare these two screening methods based on the total group of 10 820 pregnant women. In this group, I have demonstrated 57 foetuses with trisomy 18. The first arm of the study comprised 5688 pregnant women and 29 foetuses with trisomy 18. It used the results of ultrasound multi-parameter test based on the methodology described in **the Publication 3** with the risk cut-off values of 1/50, 1/100 and 1/300. I have called this arm the Ultrasound Screening Group. The second arm of the study-CSG (Combined Screening Group) consisted of 5132 pregnant women and 28 foetuses with trisomy 18 used results of the traditional CST. They were analyzed using the following cut-off risk values: 1/50, 1/100 and 1/300. Both arms of the study did not statistically differ in terms of trisomy 18 prevalence.
The screening methods applied in the ultrasound arm showed higher effectiveness in terms of sensitivity for trisomy 18 and the rate of false-positive results. The ultrasound test with the risk cut-off of 1/50 was characterized by DR = 89.7% at FPR = 1.3%; the cut-off of 1/100 DR = 100% at FPR = 1.6%, and the cut-off of 1/300 DR = 100% at FPR = 2.6%. In the CSG arm I respectively observed DR = 71.4% at FPR 1.7%; DR = 82.1 at FPR = 2.4%; and DR = 89.3% at FPR = 4.2%.
Analyzing the effect of maternal age on the screening effectiveness in the ultrasound arm in terms of sensitivity, I have shown a steady trend for sensitivity at the level of 100% for all ages using the cut-off of 1/100 and 1/300. In contrast, with the cut-off of 1/50 in the same arm I have observed a decrease in sensitivity between 26 and 40 years of age, the most expressed at the age of 31-35 years when it reached 83.3%. The rate of false positive results in this arm showed was low in all age groups, reaching up to 6.6% over 41 years. On the other hand, the CSG arm showed high correlation between the screening effectiveness and maternal age. For the cut-off of 1/300, the CST had sensitivity of 75% in the age groups below 26 and between 31 and 35 years. In other areas, the use of cut-off of 1/300 had sensitivity of 100%. The cut-off of 1/100 in the CST had a similar influence of age on sensitivity, except for the age group below 26 years of age, where there was a noticeable decrease in sensitivity to 25%. Compared with the previous group, the cut-off of 1/50 showed sub-optimal sensitivity. Like in the ultrasound arm, the CST has the low rates of false positive results with the highest values in the age group over 41 years of age. In this arm, FPR was 10.1% for the cut-off of 1/300, and 6% for the cut-off of 1/100.

Key findings of the Publication No. 4:

1. The use of multi-parameter ultrasound with the specific FMF algorithm for trisomy 18 with the cut-off of 1/100 is a more efficient screening tool than the conventional CST with the cut-off of 1/300 in terms of sensitivity (100% vs. 89%) and the rate of false positive results (1.6% vs. 4.2%).

2. The ultrasound trisomy 18 screening without biomarkers is not influenced by maternal age in terms of sensitivity and has the constant value of 100%, unlike the CST showing sensitivity of only 75% in the age groups below 26 years of age and between 31-35 years of age.

The scientific and practical importance of the Publication No. 4:
So far, the literature has not compared the CST with the screening method based on the only ultrasound parameters in relation to the age of the pregnant. The results of this study demonstrate that the trisomy 18 screening can be effectively performed with multi-parameter ultrasound and without biomarkers. Describing in the introduction the Polish conditions of screening I have mentioned that until this publication gynaecologists and clinical geneticists used in their everyday work the results of screening without biochemistry, which did not allow for the interpretation of sensitivity, false-positive results and the impact of maternal age on trisomy 18 screening effectiveness.

Publication No. 5
Besides the most common trisomies 21 and 18, monosomy X, or Turner syndrome is a relatively common chromosomal aberration. Because in utero vast majority of cases have substantially thickened nuchal scan in the order of 8.5 mm (Kagan et al. 2006) and often features of hydrops, so far, no specific mathematical algorithm has been developed to screen for aneploidy. Therefore monosomy X is detected as a side effect of the FMF algorithms designed for common trisomies. At the same time, the prenatal ultrasound image observed in Turner syndrome is difficult to differentiate from other chromosomal aberrations, single-gene diseases and early forms of foetal heart failure caused by extra-genetic reasons. We should also not overlook the fact that currently more common high sensitivity NIPT screening tests have limitations in the detection of Turner syndrome with the sensitivity of 88% and the rate of false positive results of 0.12%. This screening effectiveness is low compared to the sensitivity of this method for trisomy 21 of more than 99% (Gil et al. 2014). In connection with these facts, I have planned to conduct the study that I have published in The Journal of Maternal-Foetal & Neonatal Medicine, Taylor & Francis Group, United Kingdom.
The objectives of **the Publication 5** were as follows:

1. The analysis of aneuploidy positive markers and structural abnormalities in foetuses with monosomy X compared to foetuses without this chromosomal aberration;
2. The development of backward regression model based on the most common ultrasonographic parameters that occur in utero in Turner syndrome in order to identify the characteristics that are most likely to increase the probability of monosomy X in the foetus.

We analyzed 9632 foetuses, but the introduction of exclusion criteria, based mainly on gender of the foetus, reduced the study population to 5644 pregnant women and 31 foetuses with monosomy X. As for basic study parameters, the foetuses with euploidy did not statistically differ in terms of the parietal-sitting length from the foetuses with monosomy X. There were statistically significant differences in the thickness of nuchal translucency and heart rate. All foetuses with Turner syndrome had at least one aneuploidy ultrasound marker. 91.4% of foetuses without this chromosomal aberration did not demonstrate these markers. Only 25.8% of monosomy X cases had isolated markers. The most common combinations of ultrasound markers observed in this chromosomal aberration included the thickening of nuchal translucency along with congenital absence of the ductus venosus (32.5%) and thickened nuchal scan with negative a wave in the ductus venosus flow. 50% of Turner syndrome cases manifested non-cardiac anomalies compared to 0.95% of euploidy. As for congenital heart defects, anomalies (including 94.1% coarctation of the aorta and 5.9% hypoplastic left heart) were confirmed in as many as 54.8% of monosomy X cases compared

to 0.5% of foetuses without this chromosomal aberration. I used the most common ultrasound parameters to develop the backward regression model, which showed statistical significance for nuchal translucency thickness above 3.5 mm (OR = 991) and the right heart dominance as a sign of the left heart defect (OR = 314).

Key findings of the Publication No. 5:

1. Ultrasonography of late first trimester is the main screening tool in the monosomy X detection in the foetus.
2. The early evaluation of the heart which is effective in the assessment of the right heart dominance manifested as the increased inflow into the right ventricle compared to the left ventricle and the clear advantage of the pulmonary arm diameter over the aortic arm diameter at the level of the projection of three vessels with the trachea is a valuable helpful element in the prenatal monosomy X detection.
3. The Turner syndrome prenatal phenotypic ultrasound picture most often includes the significant thickening of nuchal translucency, the heart rate above percentile 95, the abnormal flow profile in the ductus venosus - mainly congenital absence of the ductus venosus, the features of hydrops and the right heart dominance.

The scientific and practical importance of the Publication No. 5:

So far, no other authors paid attention to the ultrasound characteristics of the late first trimester in foetuses with Turner syndrome, including congenital absence of the ductus venosus line and the evaluation of the right heart dominance. In my opinion, these features are important to differentiate the foetus suspected of a chromosomal aberration.

5. Discussion on the other scientific – research achievements:

My IF after obtaining PhD is **20,312 (KBN/MNiSW [Committee for Scientific Research/Ministry of Science and Higher Education - 230 pts.)**. In this period I also registered **two educational patents,** submitted **a following patent** and wrote one chapter for **an international textbook.**

Since the beginning of my work in the Department of Gynaecology and Obstetrics my research interests focus on the ultrasound diagnostic in terms of:

- imaging of the foetus with special emphasis on the early assessment of anatomy and the heart of the foetus in the late first trimester;
- the application of three-dimensional ultrasound in the examination of the foetus and gynaecology, especially in gynaecological cancers;
- the development of three-dimensional models of the normal heart and that burdened with congenital defects using the 3D printing method based on the collection of recorded volume images of the foetal heart using the technique of spatial and temporal image correlation (STIC).

In order to pursue my scientific interests I gradually improved my ultrasound diagnostic skills on the extensive material available at the referral centre which cooperates with a network of 28 hospitals in the region of the southern Poland. In addition, I constantly improved my skills during numerous training courses and domestic and foreign internships, including: internship in the Laboratory of Perinatology and Foetal Cardiology of the II Department of Obstetrics and Gynaecology, Medical University of Warsaw (2004); internship in the Tennessee Woman's Care Ultrasound Office, Nashville in the United States under the direction of Prof. P. Jeanty, (2006); internship in invasive ultrasonography procedures and foetal echocardiography at Yale University - Foetal Maternal Medicine Department, New Haven, United States of America under the direction of Prof. J. Copel (2006); internship in

the Department of Foetal Medicine at King's College Hospital in London (Harris Birthright Research Centre for Foetal Medicine) in invasive procedures during pregnancy (2008) completed with the practical exam and obtaining a certificate of competence in this field. In the years 2008-2009 I worked as a specialist registrar at the Department of Foetal Medicine, Imperial College in London, perfecting my skills and participating in research projects.
I gradually presented my scientific observations at national and international congresses of obstetric-gynaecological ultrasonography organized, among others, by the Polish Society for Ultrasonography; the Polish Medical Society of Radiology; the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG).

A. Three-dimensional prints of the normal foetal heart and that affected by congenital defects dedicated to the education of physicians in the prenatal cardiac ultrasound and consulting patients with congenital heart defects diagnosed before birth:

It is an original scientific achievement, which I could realize on the basis of my own extensive library of three-dimensional ultrasound images of the foetal heart and in collaboration with the GRID design studio from Krakow. The uniqueness of this project results from the use of models of the foetal heart divided into layers in line with prenatal ultrasound projections and their consistency obtained thanks to the use of magnets placed in each layer. These features allowed me to obtain the following patents:

1. For the European Union countries under the number 002834531-0001 obtained on 23/10/2015 at the Office for Harmonization in the Internal Market (Trade Marks and Design) OHIM - http://oami.europa.eu and;
2. For the United States of America (The International Bureau of the Intellectual Property Organisation) under the number DM/090 269 obtained on 01/12/2015 www.wipo.int

Together with the GRID studio I have developed 4 types of printouts of the normal heart dedicated to training purposes: 2 hearts with their axes directed to the left with the transverse and sagittal cross sections and 2 hearts with their axes directed to the right with the transverse and sagittal cross sections.
The following models of congenital heart defects were created: hypoplastic left heart syndrome with mitral valve atresia (HLHS-MA); hypoplastic left heart syndrome with aortic atresia (HLHS-AA); valvular aortic stenosis (AS); critical aortic stenosis (Critical AS); coarctation of the aorta (CoA); interrupted aortic arch (IAA); double inlet left ventricle (DILV); partial anomalous pulmonary venous return (PAPVR); total anomalous pulmonary venous return in three variants: supracardiac, cardiac and infracardiac (TAPVR); Ebstein syndrome (EA); atresia of the pulmonary valve with the continuous septum (PAIVS); atresia of the tricuspid valve type I and II (TA); tetralogy of Fallot (ToF); transposition of the great arteries type d (d-TGA); transposition of the great arteries type l (l-TGA); common arterial trunk (CAT); double outlet right ventricle of the type of Fallot and Taussig-Bing type (DORV); right-hand arch of the aorta in the variants with left and right arterial duct (RAA); double aortic arch (DAA); atrio-ventricular defect of the total and partial type (AVSD); and ventricular septal defect in three variants: inlet, trabecular and outlet (VSD).

Myself presented the application of abovementioned foetal heart 3D models in teaching of the foetal cardiac scan at the 26th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Rome 2016:

1. **Wiechec M,** Nocun A, Knafel A. OC14.04. Understanding of congenital heart defects by STIC training and 3D-printed fetal heart models. Ultrasound Obstet Gynecol 2016; 48:26. 26th

World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Rome 2016.

B. The use of three-dimensional ultrasound in obstetrics and gynaecology:

Developing my competence in three-dimensional diagnostic ultrasound, I presented my examination results at congresses and scientific seminars. Then, I was invited to write a chapter in an international textbook edited by Prof. A. Kurjak and Prof. F. Chervenak.

– **Wiechec M**, Nocun A, Beithon J. Application of Spatial and Temporal Image Correlation in the Fetal Heart Evaluation. In Donald School Textbook of Ultrasound In Obstetrics & Gynecology Third Ed. Kurjak A, Chervenak FA. Jaypee Brothers Medical Publishers 2011: 333-360.

Five years after the publication, editors of the next issue of the manual invited me again to write a chapter from the perspective of my further experience in three-dimensional foetal heart ultrasound:

– **Wiechec M**, Nocun A. Spatial and Temporal Image Correlation and other volume ultrasound techniques in the fetal heart evaluation after 10 years of practice. In Donald School Textbook of Ultrasound In Obstetrics & Gynecology 4th Ed. Kurjak A, Chervenak FA. Jaypee Brothers Medical Publishers 2016: 333-357.

After reading my reports on modern three-dimensional ultrasound techniques in obstetrics and gynaecology, the President of the Polish Society of Ultrasonography,
Prof. W. Jakubowski invited me to develop the first Polish standards on three-dimensional examinations in obstetrics and gynaecology, which appeared under the title "The Ultrasound Standards of the Polish Ultrasonography Society" in 2011:

1. **Wiechec M**, Nocun A. Standardy diagnostycznego badania 3D w położnictwie. w Standardy badań ultrasonograficznych Polskiego Towarzystwa Ultrasonograficznego (red. Jakubowski W). Warszawa, Zamość 2011.
2. Nocun A, **Wiechec M**. Standardy diagnostycznego badania 3D w ginekologii. w Standardy badań ultrasonograficznych Polskiego Towarzystwa Ultrasonograficznego (red. Jakubowski W.). Warszawa, Zamość 2011.

Based on the experience in three-dimensional imaging I have developed an innovative prenatal classification of images in complete agenesis of the corpus callosum and on this basis I have proposed a model of the foetal brain study dedicated to this one the most common congenital defects of the central nervous system. I have described this method in Ultraschall in der Medizin, Thieme, Germany.

– **Wiechec M**, Nocun A, Knafel A, Beithon J, Stettner D. Four Steps in Diagnosing Complete Agenesis of the Corpus Callosum in Prenatal Life. Ultraschall in Med 2016; 37: 92-99

IF – 4,95; KBN/MNiSW – 40 pts. *(original paper)*

Further publications on the use of three-dimensional ultrasound of my participation:
Congress reports on three-dimensional ultrasonography:

1. Nocuń A., Pityński K, **Wiecheć M**, Ludwin A, Jach R, Knafel A, Pietrus M, Kszyk Z. Wartość trójwymiarowego obrazowania wielopłaszczyznowego (MPV)

i kontrastowego (VCI) w ultrasonograficznej ocenie patologii błony śluzowej jamy macicy. Prz. Lek. 2012; 69:1271-1275.

2. **Wiechec M**, Nocun A. 3D Ultrasound Diagnostics in Contemporary Obsetrics and Gynecology. Moderni Gynekologie a Porodnictvi 2012; 21: 440-458.
3. Panek D, Stangel-Wójcikiewicz K, Nocuń A., **Wiechec M**, Petko M. Segmentacja cewki moczowej na obrazach MRI i USG w Projektowanie mechatroniczne: zagadnienia wybrane. Akademia Górniczo-Hutnicza, Kraków 2015.

Oral presentations at professional conferences:

1. **Wiechec M**, Nocun A, Knafel A. Complete agenesis of corpus callosum. 3D-ultrasound based simple diagnostic approach and a new second trimester prenatal classification. Obstetrica si Ginecologia 2013; 59: 5. 10th National Congress of Perinatal Medicine, Cluj-Napoka, Romania.
2. **Wiechec M**, Nocun A. OP08.02: Early fetal heart assessment using 4D ultrasound - STIC technique in 11-13 + 6 scans. Ultrasound Obstet Gynecol 2008; 3: 333.
   18th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Chicago 2008.
3. **Wiechec M**, Nocun A. P05.11: 3D ultrasound in complete agenesis of corpus callosum. Ultrasound Obstet Gynecol 2009; 34: 195. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.
4. Gardiner HM, Matsui H, Gindes L, **Wiechec M**, Mohun T, Ho SY, Achiron R. OP28.01: Pilot study comparing ex-vivo HREM imaging and in-vivo 4DHRTV ultrasound of the first trimester human fetal heart. Ultrasound Obstet Gynecol 2009; 34: 152. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.

C. Ultrasound examination of the early anatomy and foetal function in the late first trimester:

One of my most important research issues is the evaluation of the diagnostic effectiveness of detailed ultrasound performed in late first trimester of pregnancy, with particular emphasis on the early assessment of the heart. My studies in this field produced a number of congress reports, demonstration publications and original works, which partially contributed to my doctoral dissertation. I have introduced to the literature the method for detection of congenital heart defects in the first trimester based on the patterns of inflows into the ventricles compared with the patterns of the three vessels and trachea view mapped using the Doppler colour. Currently, this method has the highest sensitivity in the detection of congenital heart diseases at an early stage of the foetal development compared to the methods published by other authors (Wiechec M 2015; Khalil A & Nicolaides KH 2013). My research on the functional aspects in the late first trimester demonstrated that the presence of isolated tricuspid regurgitation or abnormal flow profile through the ductus venosus are usually clinically insignificant observation most likely indicating the immaturity of cardiovascular

system of the foetus. Any comparison of these functional features with additional aneuploidy ultrasound markers significantly increases its risk or the incidence of congenital heart defects.

Publications:

1. **Wiechec M**, Nocun A, Matyszkiewicz A, Wiercinska E, Latala E. First trimester severe ductus venosus flow abnormalities in isolation or combination with other markers of aneuploidy and fetal anomalies. J Perinat Med 2016; 44: 201-209. **IF – 1.79; KBN/MNiSW – 25 pts.** *(original paper)*
2. **Wiechec M**, Nocun A, Wiercinska E, Beithon J, Knafel A. First trimester tricuspid regurgitation and fetal abnormalities. J Perinat Med 2015; 43: 597-603. **IF – 1.79; KBN/MNiSW – 25 pts.** *(original paper)*
3. **Wiechec M**, Knafel A, Nocun A. Prenatal detection of congential heart disease at 11-13 weeks scan using a simple protocol of color Doppler of the four-chamber-view and the three-vessel and trachea view. J Ultrasound Med 2015; 34: 585-594. **IF – 1.53; KBN/MNiSW – 25 pts.** *(original paper)*
4. **Wiechec M**, Nocun A, Stettner D. Diagnostic Concept for Detecting Congenital Heart Defects in the First Trimester: Principles of Pattern Recognition. OMICS J Radiol 2015, 4:5 http://dx.doi.org/10.4172/2167-7964.1000207
5. **Wiechec M**, Nocun A, Beithon J. Early Fetal Echocardiography at the Time of 11+0 – 13+6 Weeks Scan. Donald School J Ultrasound Obstet Gynecol 2009; 3: 75-81

Oral presentations at conferences:

1. **Wiechec M**, Nocun A. OP01.03: Discrepancies between nuchal translucency measurements in neutral fetal position in quiescence and during spontaneous movement. Ultrasound Obstet Gynecol 2008; 32: 308. 18th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Chicago 2008.
2. **Wiechec M**, Nocun A. OP20.03: Early anomaly scan and early fetal echocardiography—effectiveness at 11 − 13 + 6 weeks. Ultrasound Obstet Gynecol 2009; 34: 125. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.
3. **Wiechec M**, Nocun A. Early Fetal Echocardiography updated and simplified. Can we adopt early cardiac evaluation into the nuchal scan? Obstetrica si Ginecologia 2013; 59: 6. 10th National Congress of Perinatal Medicine, Cluj-Napoka, Romania.
4. **Wiechec M**, Nocun A. Tricuspid regurgitation at 11-14 weeks scan. Is this a transient phenomenon or an indicator of pathology? Obstetrica si Ginecologia 2013; 59: 21. 10th National Congress of Perinatal Medicine, Cluj-Napoka, Romania.
5. **Wiechec M**, Nocun A, Knafel A. Diagnostyka USG płodu. Polish Journal of Radiology

2013; 78: 55. 40th Congress of Radiology, Wroclaw 2013.

6. **Wiechec M**, Nocun A. OC15.05: Tne role of simple protocol based on 4CV and 3VTV in color mapping at the time of nuchal scan in diagnosing congenital cardiac defects. Ultrasound Obstet Gynecol 2013; 42: 31. 23th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Sydney 2015.
7. **Wiechec M**, Nocun A, Knafel A. OC02.02: Conotruncal anomalies: how effective is first trimester diagnosis? Ultrasound Obstet Gynecol 2014; 44: 3. 24th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Barcelona 2014.
8. **Wiechec M**, Nocun A, Knafel A. Stettner D. OP18.10: First trimester "Y sign" at the level of three-vessel and trachea view: a new sensitive early marker of tetralogy of Fallot and Fallot-like double outlet right ventricle. Ultrasound Obstet Gynecol 2015; 46: 108-109. 25th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Montreal 2015.

D. Ovarian tumour ultrasound in the application of the simple rules system by IOTA (The International Ovarian Tumour Analysis):

I participated as one of the main researchers at the expert level in the two-year study conducted at the Department of Gynaecology and Oncology, Jagiellonian University, which comprised 226 patients with ovarian tumours, including 36.3% with malignancies. The work has been accepted for publication in the Ultraschall in der Medizin - European Journal of Ultrasound (Thieme, Germany).

– Knafel A, Banas T, Nocun A, **Wiechec M**, Jach R, Ludwin A, Turek M, Pietrus M, Pityński K. The prospective external validation of IOTA Simple Rules in the hands of level I and II examiners. Ultraschall in der Medizin / European Journal of Ultrasound 2016;37:516-523.
IF – 4,95; KBN/MNiSW – 40 pts. *(original paper)*

E. The use of intraoperative transrectal ultrasonography in monitoring hysteroscopic myomectomy:

I performed some ultrasound examinations at to support the difficult hysteroscopic resection of submucous myomas [a G2 degree by the ESH classification] (*The European Society of Hysteroscopy*), which in more than 50% penetrated into the wall of the uterus. This is the original method unique in the world was developed by Dr. Artur Ludwin in the Department of Gynaecology and Oncology of the Jagiellonian University. The work in his research team resulted in the publication in the *Journal of Minimally Invasive Gynaecology, Elsevier Science, United States*:

– Ludwin A, Ludwin I, Pityński K, Basta P, Basta A, Banas T, Jach R, **Wiecheć M**, Grabowska R, Stangel-Wójcikiewicz K, Milewicz T, Nocuń A. Transrectal ultrasound-guided hysteroscopic myomectomy of submucosal myomas with a varying degree of myometrial penetration. J Minim Invasive Gynecol. 2013; 20: 672-85.

IF – 1,575; KBN/MNiSW – 25 pts. *(original paper)*

Together with GRID Design Studio and Dr. Andrzej Zmaczynski (University Hospital in Krakow) I produced a hysteroscopy training set. Patent pending No. 003373232, submitted on 9th of September 2016 at *Office for Harmonization in the Internal Market (Trade Marks and Design) OHMI.*

The summary of scientific achievements:

My total to date scientific achievements comprise **58** positions, including **22** full-text original publications in foreign and domestic peer-reviewed journals, including **14** full-text publications in journals with the Impact Factor, **6** chapters in textbooks, **8** review articles,
6 case reports, **15** published congress abstracts, and **2** patents.

The total impact factor of all my full-text publications is **IF = 30,777 (KBN/MNiSW = 441,5 pts.; IC=93,58)**. The number of citations: **40** (Web of Science Core Collection of 26/08/2016), **92** (Google Scholar). The Hirsch factor according to the database Web of Science is: **2**.

6. Oral communications at international and national thematic conferences:

My research was presented in the form of oral communications at international and national conferences. The total delivered was 15. Most of them were lectures given on an international scale, including 10 presented at international congresses of ISUOG,
and 2 national oral communications.

INTERNATIONAL CONFERENCES:

1. **Wiechec M**, Nocun A. OP01.03: Discrepancies between nuchal translucency measurements in neutral fetal position in quiescence and during spontaneous movement. Ultrasound Obstet Gynecol 2008; 32: 308. 18th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Chicago 2008.
2. **Wiechec M**, Nocun A. OP08.02: Early fetal heart assessment using 4D ultrasound - STIC technique in 11-13 + 6 scans. Ultrasound Obstet Gynecol 2008; 3: 333. 18th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Chicago 2008.
3. **Wiechec M**, Nocun A. P05.11: 3D ultrasound in complete agenesis of corpus callosum. Ultrasound Obstet Gynecol 2009; 34: 195. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.
4. Gardiner HM, Matsui H, Gindes L, **Wiechec M**, Mohun T, Ho SY, Achiron R. OP28.01: Pilot study comparing ex-vivo HREM imaging and in-vivo 4DHRTV ultrasound of the first trimester human fetal heart. Ultrasound Obstet Gynecol 2009; 34: 152. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.
5. **Wiechec M**, Nocun A. OP20.03: Early anomaly scan and early fetal echocardiography—effectiveness at 11 − 13 + 6 weeks. Ultrasound Obstet Gynecol 2009; 34: 125. 19th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Hamburg 2009.
6. Wiechec M, Nocun A. Early Fetal Echocardiography updated and simplified. Can we adopt early cardiac evaluation into the nuchal scan? Obstetrica si Ginecologia 2013; 59: 6.
10th National Congress of Perinatal Medicine, Cluj-Napoka, Romania.
7. **Wiechec M**, Nocun A, Knafel A. Complete agenesis of corpus callosum. 3D-ultrasound based simple diagnostic approach and a new second trimester prenatal classification. Obstetrica si Ginecologia 2013; 59: 5. 10th National Congress of Perinatal Medicine, Cluj-Napoka, Romania.
8. **Wiechec M**, Nocun A. Tricuspid regurgitation at 11-14 weeks scan. Is this a transient phenomenon or an indicator of pathology? Obstetrica si Ginecologia 2013; 59: 21. 10th

National Congress of Perinatal Medicine, Cluj-Napoka, Romania.

9. **Wiechec M**, Nocun A. OC15.05: The role of simple protocol based on 4CV and 3VTV in color mapping at the time of nuchal scan in diagnosing congenital cardiac defects. Ultrasound Obstet Gynecol 2013; 42: 31. 23rd World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Sydney 2013.
10. **Wiechec M**, Nocun A, Knafel A. OC02.02: Conotruncal anomalies: how effective is first trimester diagnosis? Ultrasound Obstet Gynecol 2014; 44: 3. 24th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Barcelona 2014.
11. **Wiechec M**, Nocun A, Knafel A. Stettner D. OP18.10: First trimester "Y sign" at the level of three-vessel and trachea view: a new sensitive early marker of tetralogy of Fallot and Fallot-like double outlet right ventricle. Ultrasound Obstet Gynecol 2015; 46: 108-109. 25th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Montreal 2015.
12. **Wiechec M**, Nocun A, Knafel A. OC14.04. Understanding og congenital heart defects by STIC training and 3D-printed fetal heart models. Ultrasound Obstet Gynecol 2016; 48:26. 26th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Rome 2016.
13. Ludwin I, Ludwin A, **Wiechec M**, Nocun A, Banas T, Basta P, Pitynski K. Accuracy of 2D/3D high-definition flow imaging HyFoSy and 2D/3D HyFoSy in comprarison to 2D air/saline HyCoSy and laparoscopy. OP22.02 Ultrasound Obstet Gynecol 2016;48:122. 26th World Congress of International Society of Ultrasound in Obstetrics and Gynecology, Rome 2016.

DOMESTIC CONFERENCES:

1. Karasińska-Siepak K, Kalita J, Kempf-Haber M, **Wiecheć** M, Kula M, Zdebski Z. Doppler and biometric analysis of fetal hypotrophy not resulting from maternal hypertension. Ultrasonografia 2002; 8:87. 14th Congress of European Federation of Societies for Ultrasound in Medicine and Biology and VI Scientific Congress of Polish Ultrasound Society, Warsaw, 4th-7th July 2002.
2. **Wiechec M**, Nocun A, Knafel A. Diagnostyka USG płodu. Polish Journal of Radiology 2013; 78: 55. 40th Congress of Radiology, Polish Medical Society of Radiology, 2013.

7. Teaching and popularization of achievements and information on international cooperation:

A) I participated in international educational programs and other forms of international cooperation with the relevant teaching and popularization meaning:

- since 2015 annual seminar lecturer Expert in Foetal Medicine, organized by Imperial College, London, United Kingdom;

- in 2014 lecturer in the project of the European Union cross-border fund: Timisoara (Romania) - Vrsac (Serbia) "PRENATAL DIAGNOSIS NETWORK", project code MIS-ETC 1347;

- 2009-2014 activities in the international schools of ultrasonography in Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, UAE, Greece, Spain, Qatar, Kuwait, Macedonia, Nigeria, Romania, Serbia, Slovakia, the United States, Sweden, Turkey, Hungary, the UK (The Ian Donald International School of Ultrasound; IAMU-VISUS International Academy of Medical Ultrasound and International School of Three-Dimensional Ultrasound in Vienna);

- 2013-2014 Human Capital, National Cohesion Strategy, Project co-financed by the European Union within the framework of the Social Fund, Postgraduate Medical Centre in

Warsaw and Medical Centre of Postgraduate Education at the Jagiellonian University as a lecturer in specialization courses in gynaecological oncology ultrasound;

- since 2010 I have worked with the Roztoczańska School of Ultrasonography as scientific head of the training "Three-dimensional ultrasound in obstetrics and gynaecology";

- since 2004 I have taught at the Centre of Postgraduate Medical Education UJ doctors during specialization in obstetrics and gynaecology, radiology and clinical genetics in the field of gynaecology and obstetric ultrasound;

- 2006-2007 - I helped in the organization of training in endoscopy Endoexpert in the Department of Gynaecology and Obstetrics, Jagiellonian University in collaboration with Karl Storz Co.;

- 2003, 2004, 2007 I conducted classes in colposcopy courses entitled inflammation in colposcopy. The Polish Society of Colposcopy and Cervical Pathophysiology. Kraków.

B) I have taken an active part in international and national scientific conferences:

1. Since 2006 as an active participant of international congresses organized by the *International Society of Ultrasound in Obstetrics and Gynaecology* (ISUOG);
2. Speaker at international congresses (*Ceska Gynekologicka a Porodnicka Spolecnost (CLS JEP), Hellenic Society for Ultrasound in Obstetrics and Gynecology; Romanian Association of Perinatal Medicine (ARMP), Romanian Society for Ultrasound in Obstetrics and Gynaecology (SRUOG)*) and national congresses of the Polish Society of Ultrasonography.
3. Attendee of scientific training conferences and congresses organized by the Polish Society for Colposcopy and Cervical Pathophysiology.

C) I was an active member of the organizing committee in international and national conferences:

1. Congress of the Polish Society of Colposcopy and Cervical Pathophysiology, 2003, Krakow, a member of the organizing committee;

2. International Congress of Colposcopy and Pathophysiology of the Lower Female Genital Tract for the Central and Eastern European Countries, 2003, Kraków 2003, a member of the organizing committee;

3. Polish-German Congress "New perspectives in the diagnosis and treatment of certain gynaecological oncology diseases ", 2011 Krakow, a member of the organizing committee;

4. IX Symposium "Current Problems of Perinatology", 2016 Zakopane, a member of the organizing committee.

D) Other achievements in teaching and popularization of science or art:

1. Two-disc practical educational DVD recording entitled Wiechec M. "Introduction to the effective diagnostic application of clinical features on the Voluson Signature Series"

2011, General Electric Company, Zipf, Austria on the application of modern three-dimensional imaging techniques of the foetus in the palate bone, body, heart, spine and brain; as well as defects of the uterus and the volume of ovarian follicles. This recording was distributed among General Electric camera users and is available in the Internet. Volusonclub 2011, General Electric Company, Zipf, Austria;

2. Technical development: A. Nocuń, M. Wiecheć "Application of transabdominal STIC colour in the first trimester" Volusonclub White Paper Collection 2010, General Electric Company, Solingen, Germany: 51-57. This is optimal from the point of view of an examiner technical description of the three-dimensional recording method of the foetal heart in the first trimester using the technique of time-space correlation image mapped with the colour Doppler.

3. Development of ultrasound educational posters in collaboration with Holbex Co.:

- The early examination of foetal anatomy (11 weeks + 0 days to 13 weeks + 6 days) (2013);
- The foetal anomaly scan in the second trimester (2014).

E) Scientific supervision over students and doctors in specialization:

- Director of OB/GYN speciality program in obstetrics and gynaecology for one trainee: 2012-2015; Department of Obstetrics and Perinatology, University Hospital in Krakow.

8. Awards and honours:

1. 2016-second place in the Gazeta Krakowska competition "Man of the Year" for the development of three-dimensional model of the foetal heart, together with Dr. Agnieszka Nocuń and Assoc. Prof. Jacek Kołcz.

2. I have obtained the status of honorary member of two societies:
- 2013: Romanian Association of Perinatal Medicine (ARMP);
- 2016: Romanian Society for Ultrasound in Obstetrics and Gynaecology (SRUOG).

9. Directing research projects:

I am currently not managing any research project.

10. Reviewing publications in international and national journals:

I am a reviewer in two foreign scientific journals of the international scope:
1. *Foetal Diagnosis and Therapy, Karger AG, Basel, Switzerland;*
2. *Actual Gynaecology and Obstetrics, Prague, Czech Republic*

11. Membership in international and national organizations and scientific societies:

1. Polish Ultrasound Society

- since 2010, member,
- since 2014 Chairman of the Section of Obstetrics, Prenatal Diagnostics and Gynaecology;

2. International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG)

- since 2006, member,
- since 2015 currently the only representative of Poland - International Faculty Member;

3. Romanian Association of Perinatal Medicine (ARMP), honorary member;

4. Romanian Society for Ultrasound in Obstetrics and Gynaecology (SRUOG), honorary member;
5. Polish Gynaecological Society, since 2001, member;
6. The International Prenatal Screening Group, member;
7. The American Institute of Ultrasound in Medicine, international e-associate.

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Marcin Wiecheć MD, PhD