

# CAN INFLAMMATORY MARKERS DIAGNOSED UPON ULTRASOUND EXAMINATION DURING PREGNANCY REGRESS AFTER ADMINISTRATION OF VAGINAL TREATMENT? – A PILOT STUDY



**Authors:**  
Maria Szubert<sup>1</sup>, Maria Respondek-Liberska<sup>2,3</sup>

1. Medical University of Lodz, Poland, Department of Obstetrics and Gynecology 2. Department of Prenatal Cardiology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland 3. Department of Diagnoses and Prevention Fetal Malformations Medical University of Lodz, Poland

PRENAT CARDIO. 2015 JUN;5(2):11-14  
DOI 10.12847/06152

## Abstract

**Background:** Inflammatory markers in prenatal ultrasound are a heterogeneous group of images that can evolve during pregnancy, due to regression or exacerbation of infection in pregnant women.

**Objective:** The assessment if effective rebalancing of the bacterial flora of the vagina can lead to withdrawal of the symptoms of inflammation in ultrasound examination (US).

**Methods:** A retrospective pilot study, among pregnant woman admitted to the Department of Prenatal Cardiology ICZMP in 2013-2014 in whom ultrasonographic signs of intrauterine infection were present. Electronic database were searched for key words "infection, placentitis, tricuspid regurgitation, poly/oligohydramnion, IUGR, CRP, antibiotics, vaginal treatment". The analysis included 238 patients, 30 received antibacterial vaginal treatment, from 27 patients a complete follow-up (control ultrasound after 10-14 days and data on labor) were obtained.

**Results:** The average age of patients was 29 years. In 22% of patients tricuspid regurgitation was observed and it was the most commonly recognized marker of infection. Regression of infection signs were observed in 21 patients (77.8%) after 2 weeks of vaginal treatment.

2 patients presented with ultrasound image stabilization, in 3 patients worsening of tricuspid regurgitation or cardiac hypertrophy were detected. Polyhydramnios, the second most common parameter (18.51% of patients) resolved after treatment in all studied patients. The delivery took place an average at 39th week of gestation (SD +/- 1.93).

**Conclusions:** Effective anti-inflammatory vaginal treatment improved ultrasound images in 21 out of 27 fetuses. These preliminary observations suggesting a beneficial role of the vaginal treatment on inflammatory markers in pregnancy ultrasound require further investigation.

**Key words:** tricuspid valve regurgitation, polyhydramnion, heart failure, pregnancy, inflammation

## INTRODUCTION

Markers of inflammation observed in prenatal ultrasound are a large group of small features that are interpreted together as ultrasound markers of intrauterine infection. These markers include placenta thickening, tricuspid regurgitation, pericardial effusion and effusion in other body cavities of the fetus, increased or decreased amniotic fluid, abnormal echogenicity of fetal liver and intestine, calcification foci in the CNS or bright spot in fetal heart<sup>1-5</sup>. These markers are non-specific, i.e. there is no one particular state, which may cause them to occur. Pregnant women may be exposed to a variety of infectious agents, usually viral, depending on the

### How to cite this article:

Szubert M,  
Respondek-Liberska M.:  
*Can inflammatory markers diagnosed upon ultrasound examination during pregnancy regress after administration of vaginal treatment? – a pilot study.*  
*Prenat Cardio. 2015 Jun;5(2):11-14*



season, lifestyle, job description, contact with children. In the group of pregnant women more common are infections of the upper respiratory tract, including those caused by cytomegalovirus (CMV) or influenza virus, urinary tract infections or vaginal infections i.e. bacterial vaginosis or candidosis. Data regarding inflammation signs in prenatal US

scans comes from retrospective studies or case reports and its relationship to the kind of maternal infection is poorly understood. We asked ourselves an easy question – can the effective rebalancing of bacterial flora of the vagina lead to the withdrawal of inflammation symptoms in ultrasound examination?

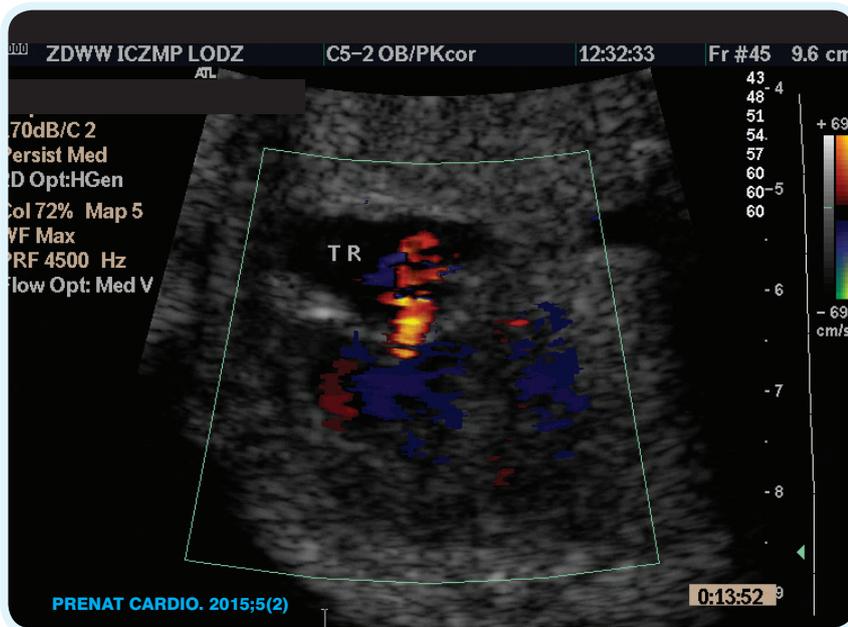


Figure 1. Color doppler assesment of tricuspid regurgitation in fetus in 27 week of pregnancy.

**AIM OF THE STUDY**

The aim of the study was to assess ultrasound markers of intrauterine infection in fetuses who for various reasons were under the care of the Department of Prenatal Cardiology ICZMP, before and after treatment with maternal vaginal anti-inflammatory drugs.

**METHODS**

Retrospective data was collected from pregnant women referred to our unit for various reasons within the years 2013-2014. 238 images suggesting infection in ultrasonography were obtained. The following possible symptoms of infection were taken into consideration: polyhydramnios, oligohydramnios, heart valve insufficiency, hyperechoic focus („bright spot”) in the heart, fluid in the body cavities of the fetus, placenta thickening (> 5 cm), hyperechogenic bowel, pyelectasis. Women with severe heart failure of the fetus as well as women with twin gestation or treated with beta-mimetics for preterm delivery were excluded from the study. Evaluation of amniotic fluid index (AFI) was made by Phelan<sup>6</sup>. 30 patients with signs of infection in US, who received vaginal treatment and came for a follow-up visit were analysed. Vaginal treatment was dependent on the decision made by leading obstetrician and obtained data indicated that the following globules were used: Macmiror, Clotrimazol, Gynalgin, Gyno-Femidazol, Vitagyn C, Lacibios Femina, vaginal gel (Abiofem), lactobacilli

(without known trade name). However, the individual influence of each of the medications used, were not evaluated by ultrasound. Follow-up (control ultrasound after 10-14 days and data on birth) was obtained from 27 patients and the study group was statistically analyzed (Ms Excel 2013, t-student test, p value <0,05 was considered to be statistically significant).

**RESULTS**

The average age of diagnosed patients was 29 years. First visit to our unit occurred between 19 and 31 weeks of gestation. Data relating to pregnancy and childbirth are shown in Table 1. 6/27 patients (22%) were diagnosed with only one abnormality, which was most often tricuspid regurgitation (Figure 1). Tricuspid regurgitation was also the most frequently observed marker of infection in the whole group detected in 16 of 27 patients (59.26%). The incidence of

other infection markers are shown in Table 2. In addition, individual subjects had symptoms of infection of the CNS (hyperechoic brain tissue, occipital tumor filled with fluid), pericardial effusion and cardiac arrhythmias. The regression of typical infection signs were observed at the follow-up ultrasound in 21 patients diagnosed upon ultrasound examination for infection and treated with vaginal medication. Two patients presented with the same sonographic image, three patients presented with worsening symptoms of infection: in the form of deterioration of tricuspid regurgitation (2 x), and the appearance of cardiac hypertrophy (1 x) – table 3.

**DISCUSSION**

It is known that an infectious agent may be a risk factor for preterm delivery<sup>5,6</sup>. Regardless of the gestational age

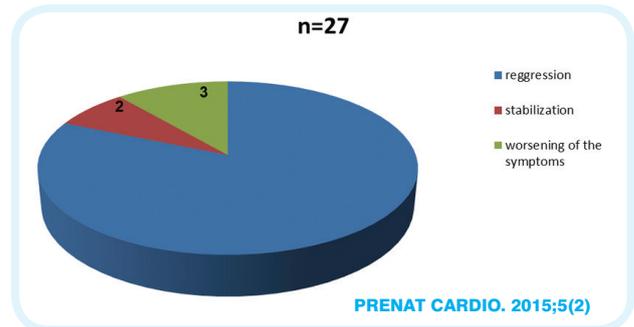


Figure 2 Control ultrasound examination after vaginal treatment.

Mean maternal age	Gestational age at the time of the diagnosis at the referral center(mean)	Delivery (data from n=24 patients; 3 losts to follow-up)	Time of gestation at delivery	Mean birth weight (g) (n=24)	Apgar scale
29 years	26 week of gestation	54% cesarean sections (n=13)	39 +/-1,93	3060 +/- 622 Median 3000	9,15 +/-0,874

Tab. 1. Perinatal outcomes in the studied group (n=27)

two so-called primary markers, assess risk of preterm delivery: cervical shortening calculated by ultrasound and the concentration of fetal fibronectin in the cervical mucus<sup>6</sup>. Secondary risk factors include: bacterial vaginosis (BV infection) and elevated levels of proinflammatory cytokines, predominantly IL-6, ferritin and granulocyte colony stimulating factor (GCSF) in cervical mucus. Population at high risk for preterm labor is often subjected to complex, multifactorial screening schemes, which if possible, include measurements of the mentioned cytokine levels. In the population at low-risk for preterm delivery the sensitivity of described methods is still unsatisfactory. For this reason, researchers are looking for various other markers of inflammation, which could be easily visible upon ultrasound examination. This analysis considered the changes in ultrasound images assessed as „typical for infection” after effective anti-inflammatory vaginal treatment of pregnant women.

Polyhydramnios is one of the known ultrasound markers of infection. According to the definition it is an excessive accumulation of amniotic fluid, which is found in one of 200 pregnant women [[http://fetalmedicine.org/var/uploads/18-23\\_Weeks\\_Scan.pdf](http://fetalmedicine.org/var/uploads/18-23_Weeks_Scan.pdf)]. The diagnosis

of polyhydramnios is usually made subjectively. Quantitatively it is defined as an amniotic fluid index (AFI) of 20 cm or more (AFI – the sum of the vertical measurements of the largest pockets in the four quadrants of the uterus). Historically it was first described and implemented into routine use by Phelan in 1987<sup>6</sup>. Because AFI measurement is subjective, it should be repeated and verified at next ultrasound examination to avoid over diagnosis and unnecessary interventions. Observations of polyhydramnios made for over twenty years confirmed associations of these finding with malformations of the fetuses, but still around 80% of cases of polyhydramnios fail to identify the causes of its origin<sup>7-10</sup>. Kouame N et al.<sup>11</sup>, analysed a group of 3,000 pregnant women in Africa of which 72 cases of polyhydramnios were detected, and in 17 of those the cause was not clearly established. The authors conclude that polyhydramnios is an important warning of under-diagnosed viral infections in pregnant women. On the other hand, these infections can be transient, with short-term resistance (like after infection with influenza virus and parainfluenza), and the detection of antibodies at the time of diagnosis of polyhydramnios could be unreliable<sup>12</sup>. In our material at first ultrasound examination polyhydramnios presented in 19% of patients (n = 5), at



Scan the code using your mobile device to get access to the pdf file instantly



Bright Spot LV/RV Left Ventricle/ Right Ventricle	7/27 (25,9%)
Tricuspid valve regurgitation	16/27 (59,26%)
Other regurgitation (atrioventricular; pulmonary)	5/27 (18,51%)
Polyhydramnios (AFI>18)	5/27 (18,51%)
Oligohydramnios (AFI<6)	2/27 (7,4%)
Placenta thickening > 5 cm	3/27 (11,1%)
Pyelectasis	3/27 (11,1%)
Increased liver echogenicity	1/27 (3,7%)
Hyperechogenic intestine	1/27 (3,7%)

Tab. 2. The incidence of infection markers in the studied group (n=27)

follow-up visit none of the patients treated with vaginal antibacterial agents presented this sign.

Another marker visible during ultrasound, which is assigned a relationship to infection in pregnancy, is tricuspid valve regurgitation. This marker was first described by Respondek et al.<sup>13</sup>. Messing B. et al<sup>14</sup>, reported that the incidence of this disorder can be found in up to 83% of the population of pregnant women in early second trimester and in about 23% of women in the third trimester. In his material 157 pregnant women were examined and it has not been established that this defect is accompanied by genetic malformations or chromosomal changes. Researchers try to explain the occurrence of tricuspid valve regurgitation in the early second trimester by high vascular resistance of the placenta, which decreases after 16-18 weeks of gestation<sup>14</sup>. On the other hand, it plays an indisputable role in screening for trisomy 21, 13 and 18<sup>15</sup>. Other studies indicate that this anomaly is associated with infection in 3,2-6%, especially after 24 weeks of pregnancy, and the use of beta-agonists (fenoterol) in pregnancy<sup>16,17</sup>. In this period of pregnancy cyclic echocardiographic assessment of progression or regression of tricuspid regurgitation may indirectly indicate the status of the infection<sup>17</sup>. Bizjak G. analyzing the case of intrauterine fetal parvovirus B19 infection indicated that tricuspid regurgitation may occur due to functional changes caused by fetal anemia, secondary to parvovirus<sup>18</sup>. The presented material from our study group showed that tricuspid regurgitation was the most common diagnosis upon which an infection was suspected. We excluded from the analysis patients undergoing tocolysis due to its known influence on the cardiovascular system (i.e. hyperkinetic circulation, tricuspid valve regurgitation)<sup>19</sup>. Some types of intrauterine infections may result in intrauterine growth restriction (IUGR)<sup>20,21</sup>. While IUGR is diagnosed prenatally by ultrasound, postnatal infection effects, including effects on the central nervous system (CNS), are impossible to assess at the stage of pregnancy.

The role of anti-inflammatory vaginal treatment as well as its impact on the evolution of ultrasound markers of inflammation has not been sufficiently described. The advantage of our retrospective study is that according

to the search of medical databases conducted by us, it is the first of its kind. In the group treated with vaginal drugs deliveries occurred mostly at term (an average: 39 week of gestation), and the mean body birth weight was 3060 g (+/- 622 g). This fact encourages to implement a well-planned, randomized study on the effect of vaginal treatment on ultrasound image during pregnancy. Another sign, which could be associated with infection, is bright spot in the fetal heart. According to Sokolowski et al., there is a correlation between the diagnosis of bright spots and a lower birth weight<sup>22</sup>. The only limitation in the presented study is the lack of other information regarding laboratory investigations and lack of randomization. It should also be borne in mind that some of those even severe anomalies in fetuses - may regress spontaneously due to infection resolution<sup>23</sup>.

## CONCLUSIONS

Effective anti-inflammatory vaginal treatment improved ultrasound images in 21 / 27 fetuses. Preliminary observations suggest a beneficial role of vaginal treatment on regression of inflammatory markers in prenatal ultrasound but require further investigations.

### References

1. Rac MW, Bryant SN, McIntire DD, Cantey JB, Twickler DM, Wendel GD Jr, Sheffield JS.: Progression of ultrasound findings of fetal syphilis after maternal treatment. *Am J Obstet Gynecol* 2014, 14: 563-568
2. Duff P.: A thoughtful algorithm for the accurate diagnosis of primary CMV infection in pregnancy. *Am J Obstet Gynecol* 2007, 3: 196-197
3. Carlson A, Norwitz ER, Stiller RJ.: Cytomegalovirus Infection in Pregnancy: Should All Women Be Screened? *Rev Obstet Gynecol* 2010, 3: 172-179
4. Degani S.: Ultrasound in the evaluation of intrauterine infection during pregnancy. *Harefuah* 2009, 7: 460- 474
5. Kim BJ, Romero R, Mi Lee S, Park CW, Shin Park J, Jun JK, Yoon BH.: Clinical significance of oligohydramnios in patients with preterm labor and intact membranes. *J Perinat Med* 2011, 2: 131-136
6. Phelan JP, Smith CV, Broussard P, Small: Amniotic fluid volume assessment with the four-quadrant technique at 36-42 weeks' gestation. *J Reprod Med* 1987, 32: 540-542
7. Leitch H.: Secondary predictors of preterm labour. *BJOG* 2005, 1: 48-50
8. Hamza A, Herr M, Solomayer M, Meyberg-Solomayer G.: Polyhydramnios: Causes, Diagnosis and Therapy. *Geburtshilfe und Frauenheilkunde* 2013, 12: 1241-1246
9. Golan A, Wolman I, Sagi J.: Persistence of polyhydramnios during pregnancy – its significance and correlation with maternal and fetal complications. *Gynecol Obstet Invest* 1994, 37: 18
10. Pri-paz S, Khalek N, Fuchs K.M, Simpson LL.: Maximal amniotic fluid index as a prognostic factor in pregnancies complicated by polyhydramnios. *Ultrasound Obstet Gynecol* 2012, 39: 648-653
11. Kouamé N, N'goan-Domoua AM, Nikiéma Z, Konan AN, KE N'guessan, Sétchéou A, Tra-Bi ZO, N'gbesso RD, Kéita AK.: L'hydramnios. signe d'alerte au cours du diagnostic échographique anténatal d'anomalie morphologique fœtale ? *Journal de Radiologie Diagnostique et Interventionnelle* 2013, 94: 449-453
12. Fayyaz H, Rafi J.: TORCH screening in polyhydramnios: an observational study. *J Matern Fetal Neonatal Med* 2012, 25: 1069
13. Respondek M, Kammermeier M, Ludomirsky A, Weil S, Huhta JC.: The prevalence and clinical significance of fetal tricuspid regurgitation. *Am J Obstet Gynecol* 1994, 171: 1265-1270
14. Messing B, Porat S, Imbar T, Valsky DV, Anteby EY, Yagel S.: Mild tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11+0 to 13+6 weeks of gestation. *Ultrasound Obstet Gynecol* 2005, 6: 606-609
15. Kagan KO, Valencia C, Livanos P, Wright D, Nicolaidis KH.: Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11+0 to 13+6 weeks of gestation. *Ultrasound Obstet Gynecol* 2009, 1: 18-22
16. Respondek-Liberska M.: Specific and nonspecific fetal cardiac problems. *Pol Merkur Lekarski* 2004, 16: 415-419
17. Krasoń A, Janiak K, Kaczmarek P, Respondek-Liberska M.: The role of fetal echocardiography during maternal pharmacological treatment. *Ginekol Pol* 2002, 7: 645-651
18. Bizjak G, Blondin D, Hammer R, Kozłowski P, Siegmann HJ, Stressig R.: Acute infection with parvovirus B19 in early pregnancy. *Ultrasound in Obstetrics & Gynecology* 2009, 2: 234-235
19. Krasoń A, Kaczmarek P, Respondek-Liberska M.: Analiza wpływu farmakoterapii ciężarnej na występowanie niedomykalności zastawki trójdzielnej terapii tokolitycznej w porodzie przedwczesnym. *Kliniczna Perinatologia i Ginekologia* 2002, 36: 187-194
20. Bailão LA, Osborne NG, Rizzi MC, Bonilla-Musoles F, Duarte G, Bailão TC.: Ultrasound markers of fetal infection part 1: viral infections. *Ultrasound* 2005, 4: 295-308
21. Cordier A, Nedellec S, Benachi A, Frydman R, Picone O.: Arguments for an infectious cause of IUGR. *J Gynecol Obstet Biol Reprod (Paris)* 2011, 40: 109-115
22. Sokołowski Ł, Respondek Liberska M. The follow up of 114 fetuses and newborns (without chromosomal aberrations) with echogenic intracardiac focus detected in prenatal USG. *Prenat Cardio*. 2014, 4(2): 6-10. doi 10.12847/06141
23. Włoch A, Respondek M, Włoch S, Sadowski K, Kaczmarek P, Włodarska D.: Fetal functional pulmonary atresia with ascites resolving spontaneously before birth. A case report. *Fetal Diagn Ther* 1997, 12: 43-45

### Contribution of the authors in this research:

**Maria Szubert:** data search, first draft, discussion, submission

**M. Respondek-Liberska:** concept of the research, correction of the paper, final version

**Financing:** The research was not financed from the external sources

**Conflict of interest:** The authors declare no conflict of interest and did not receive any remuneration