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ORIGINAL ARTICLE

The influence of antibiotic treatment on tocolysis in threatened advanced pregnancy

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Abstract

OBJECTIVE: The aim of this study was to determine: a) to what extent application of antibiotics enhances efficiency of tocolysis; b) whether the duration of antibiotic treatment influences its efficacy; c) what criterion is decisive for efficacy of tocolysis assisted by antibiotic therapy.

MATERIALS AND METHODS: 223 successive women with unifetal pregnancies, aged 17 to 42 (average age 27.3), admitted to the Department of Gynecology and Obstetrics of the JU Medical College in the period from January 1, 1999 to September 9, 2001, were enrolled in the study. Using clinical methods such as: assessment of contractile activity of the uterus, of uterine cervix and membranes, presence of bleeding and other clinical symptoms, these women were diagnosed with imminent preterm labour.

CONCLUSIONS: Antibiotic treatment enhances the efficacy of tocolysis, influencing the time of prolonging pregnancy in imminent preterm delivery. This synergistic effect is clinically crucial as in this way significantly larger number of children will be born at term and also a number of premature neonates who survive may be increased.

Introduction

According to R. Klimek, preterm labour is a labour which takes place a week or more before the individual delivery term, calculated by a computer method [23,25,27,28,29,30]. Despite the progress in the science of obstetrics, especially in the recent years, the etiology of preterm labour has not been recognized yet and even in the developed countries it is still the main cause of perinatal morbidity of neonates. In Poland, the survival rate of babies with low birthweight is still unsatisfactory. Among children born before the twenty-seventh gestational week, only 20% survive. The frequency of preterm labours is considered to be one of the most reliable indicators of efficacy of medical treatment in a given country. In Poland, it rates from 7.2 to 8.4%, which is higher than in

France, the Netherlands and Sweden (about 4%) and lower than in the United States of America (from 7.9 to 11%) [26,42,44,47].

Identification of the factors responsible for inducing premature contractile activity of the uterus and, as a result, preterm delivery and the birth of a neonate with low or very low birthweight is extremely vital in determining the causes of incidence of preterm birth [2,3,6,28]. Low birthweight of a neonate entails not only the increase of perinatal morbidity, but also the increase in incidences of terminal diseases, such as: persistent fetal circulation, necrotic gastroenterocolitis or cerebral haemorrhage [1,12].

Despite the multifactorial nature of the etiology of preterm birth, main causes inducing this complication in pregnancy can be grouped [45] as follows:

- demographic, social and occupational factors (race, age, marital status, occupation, stress);
- genetic load (innate defects, multiple pregnancies);
- obstetric past (miscarriages, preterm labours);
- irregularities in the course of pregnancy (pathology of placenta, isthmocervical insufficiency, systemic maternal diseases);
- intrauterine infections.

Textbooks and studies published in the 1980s and 1990s point to idiopathic cause of most preterm labours – the authors could not identify the factors responsible for this complication of pregnancy [2]. However, with time, many proofs have been gathered to confirm the fact that, for example, infections of vagina and uterine cervix can be responsible for inflammation and premature rupture of membranes, as well as for preterm labour, which so far has been labeled as 'idiopathic' [3,14,44]. Infectional factor, neglected in the past, has turned out to be the main agent causing the occurrence of preterm delivery [5,10,13,17,18,34,40].

Pathogens can get to the chorionic and decidual space in three different ways: 1. Through blood and placenta in the case of systemic infection; 2. Through spreading from the inflammatory focus in abdominal cavity; 3.Through the ascending tract from vagina and uterine cervix to the chorionic and decidual space and spreading to the foetus. Nowadays, it is believed that the first two enlisted ways of infection spreading are marginal [40,41], whereas, according to M.J. Diverse and R.J. Lilford, infections of vagina and uterine cervix during pregnancy may cause even as much as 40 to 47% of preterm deliveries, and inflammatory changes were detected in 19 to 74% of examined placentas from preterm labours.

R. Romero and M. Mazor proposed the diagnosis of the degree of infection present by applying the following scale [42]:

1) development of bacterial flora in vagina and uterine cervix;
2) development of bacterial flora in decidua, chorion, amnion and foetal vessels;
3) development of bacterial flora in amniotic fluid;
4) infection of the foetus: pneumonia, gastroenterocolitis, otitis, conjunctivitis, sepsis.

Explanation of the patomechanism of preterm labour in the case of intrauterine infection is inextricably connected with understanding of a cluster of inflammatory factors released after the infection of the foetus by pathogens. Inflammation is a natural defense reaction of organism, which is released by permeation of pathogens and, in most cases, this process is self-limited. However, in certain conditions, defense mechanisms of organism can be disturbed and they can turn out to be insufficient to protect organism from injury or even damage. Intrauterine infection, often asymptomatic, releases a group of inflammatory factors stimulating synthesis of prostaglandins, which is accompanied by the decrease in the level of 15hydroxydehydrogenase (an enzyme decomposing prostaglandins) in membranes, and induces the increase in the level of metabolites, especially PGE – a factor causing contractile activity of the uterus [15]. Some bacterial strains such as Gardnerella vaginalis or Neisseria gonorrhoea, as well as streptococci from group B, synthesize phospholipase A2. This is an enzyme inducing a chain of prostaglandin-building from arachidic acid, stored as esters in membranes of phosholipidis in amnion and decidua. It can also be assumed that some microorganisms directly injure amnion and decidua, releasing synthesis of prostanoids [15]. In the case of inflammatory reaction, the first cells that respond to inflammatory stimuli are polynuclear granulocytes. This is so because under the influence of lipopolisaccharides of bacterial tissue membranes they produce large amounts of proteases such as collagenase or elastase. Collagenase, in turn, decomposes collagen – a main ingredient of connective tissue, in 85% comprising of the uterine cervix substance. This reaction induces accelerated maturing of uterine cervix, which is manifested as its shortening, retraction and change of consistency. Under the influence of lipopolisaccharides of bacterial tissue membranes, as well as the DNA of bacteria in placenta and membranes, large amounts of cytokinins such as IL-1, IL-2, IL-6, IL-8 and TNF are released. Many authors, including Romero, believe that the level of IL-6 in the blood of mother and foetus, as well as in membranes, is the most sensitive indicator of the incidence of intrauterine infection [15, 32, 41]. Uncontrolled inflammatory reaction stimulated by the production of large quantities of cytokinins plays a crucial role in the patomechanism of septic shock. In such cases it is also useful to mark the TNFalfa factor [19,43].

If any symptoms occur indicating that preterm labour may happen, appropriate diagnostics should be applied. It is possible to eliminate inducing factors, which gives a possibility of effective treatment. Thus it is vital to identify risk factors of preterm birth in each pregnant woman individually, particularly in those with unfavourable obstetric past (miscarriages and preterm delivery) [24, 35, 36, 37, 44, 45]. Such women should be referred to well equipped health centres with highly qualified staff so that preterm birth could be prevented.

According to Y. Ville, intensification and duration time of chorioamnionitis is prognostically particularly unfavourable as it is often the main cause of failure in antibiotic treatment and tocolysis in the treatment of imminent preterm delivery [28,45].

Despite much research conducted [7,8,9,16,20,21, 22,31,33,38,39], application of antibiotic treatment in the case of imminent preterm labour remains controversial and the efficiency of tocolysis needs further investigation.

Objectives

The aim of this study was to determine: a) to what extent application of antibiotics enhances efficiency of tocolysis; b) whether the duration of antibiotic treatment influences its efficacy; c) what criterion is decisive for efficacy of tocolysis assisted by antibiotic therapy.

Material and Methods

223 successive women with unifetal pregnancies, aged 17 to 42 (average age 27.3), admitted to the Department of Gynecology and Obstetrics of the JU Medical College in the period from January 1, 1999 to September 9, 2001, were enrolled in the study. Using clinical methods such as: assessment of contractile activity of the uterus, of uterine cervix and membranes, presence of bleeding and other clinical symptoms, these women were diagnosed with imminent preterm labour.

Two study groups were formed: Group A included 117 pregnant women administered tocolysis and antibiotic treatment; Group B included 106 pregnant women who were administered tocolysis only.

The use of antibiotics together with tocolysis in Group A was connected with a suspicion of developing intrauterine infection and release of amniotic fluid. The experience of the study doctor also played a crucial role here.

It was concluded that patients from study groups didn't substantially differ in terms of age, obstetric past, place of living, education, occupation and level of oxytocinase on admission to hospital.

The kind of treatment applied to pregnant women after admission depended on their clinical state (detected symptoms of intrauterine infection), on doctor's experience and on results of bacteriological investigation of secretion from uterine cervix.

In Group A, patients were administered antibiotics. The choice of antibiotics administered was either in accordance with the results of microbiological investigation, with consideration of resistance, or broad-spectrum antibiotics were applied.

Average duration of antibiotic treatment was 8.3 days (1–48 days). In the case of 29.3% of the pregnant women, antibiotics were administered for less then 3 days, in 42.7% of them – from 3 to 10 days, whereas in 28% of women antibiotic treatment lasted more than 10 days. Statistically, antibiotics were most often applied from 3 to 10 days ($p=0.02$).

In 158 cases, bacteriological investigations of uterine cervix secretion were conducted in the Bacteriological Laboratory of the Cracow University Hospital Diagnostics.

Results

It turned out that on admission to hospital patients in Group B, were on average in more advanced pregnancy, namely around the 34th gestational week (from 24th to 37th gestational week) in comparison with patients in Group A, who were admitted in the 31st gestational week (from 20th to 37th gestational week). The difference between study groups occurs with the probability $p<0.001$ (table 1 and 2).

At delivery time, patients from Group B were on average in the 35th gestational week (from 24th to 39th gestational week), whereas patients from Group A – in the 33rd gestational week (from 23rd to 41st gestational week). The difference between the groups analyzed is statistically significant at the probability level of $p<0.001$.

In Group A, 93 pregnant patients (79.5%) underwent spontaneous delivery through natural passages, 24 patients (20.5%) underwent caesarean section, one was manually assisted with the Bracht's method.

In group B, 91 pregnant patients (86.6%) underwent spontaneous delivery through natural passages, 13 patients (12.4%) underwent caesarean section. It turned out, then, that delivery type in the two study groups did not differ in a statistically significant way, Table 3. In Group A, 34 patients (29.3%) delivered within the biological norm, 77 patients (66,4%) delivered at preterm, 4 patients (3.4%) suffered from intrauterine death of foetus, one neonate died within 7 days after delivery. In Group B, 68 patients (64.8%) delivered within the biological norm, 35 patients (33.3%) delivered at preterm, in two cases (1.9%) intrauterine death of foetus took place. As can be seen from Table 3, in Group B the patients delivered within the biological norm statistically more frequently than in Group B, where, significantly, there were more preterm labours ($p<0.001$).

In Group A, 37 patients (31.9%) suffered from preterm flow of amniotic fluid, whereas in Group B this complication occurred only in 6 cases (5.9%). Between the study groups, the level of significance in the frequency of preterm flow of amniotic fluid was assessed as $p<0.001$ (table 4).

In Table 5, the duration pregnancy maintenance (from the beginning of treatment to delivery) was presented. The analysis revealed that the average duration of pregnancy maintenance in Group A was 13.7 days (from 1 to 29 days). Whereas in Group B, the average time of pregnancy maintenance was 7.3 days (from 1 to 22 days). The level of significance of the duration of pregnancy maintenance between the researched groups ($p<0.001$).

Table 1: Results of the analysis of gestation period on admission to hospital, on delivery, during hospitalization, during hospitalization, number of control visits in Group A and B during pregnancy.

Description of parameter	Group		Relevance of differences
	A	B	
	x + SD (min-max)	x + SD (min-max)	
Gestational period during hospitalization	11.1 + 4.9 (4–27)	10.5 + 5.4 (4–25)	NS
Gestational period on admission to hospital	30.6 + 3.7 (20–37)	33.4 + 2.7 (24–37)	p<0.001
Gestational period on delivery	32.7 + 4.5 (23–41)	34.8 + 3.4 (24–39)	p<0.001
Number of control visits during pregnancy	6.3 + 3.1 (1–12)	7.4 + 3.4 (1–12)	NS

Table 2: Results of the analysis of delivery type in Group A and B

Group	n	Labour type						Relevance of differences
		Vaginal labour		Cesarean section		Bracht's maneuver		
A	117	93	(79.5%)	24	(20.5%)	1	(1.0%)	Chi^2=3.654 p=0.16 (NS)
B	105	91	(86.6%)	13	(12.4%)	0	(0%)	

Table 3: Results of the analysis of the frequency of preterm deliveries, intrauterine deaths, neonatal deaths in the period of seven days after delivery in Group A and B.

	Group			
	A		B	
Labour at term	34	(29.3%)	68	(64.8%)
Preterm labour	77	(66.4%)	35	(33.3%)
Intrauterine death	4	(3.4%)	2	(1.9%)
Death during 7 days after delivery	1	(0.9%)	0	(0%)
Relevance of differences	Chi^2=28.273 (p<0.001)			

Table 4: Results of the analysis of the frequency of preterm flow of amniotic fluid in Group A and B.

Group	n	Flow of amniotic fluid				Relevance of differences
		YES		NO		
A	116	37	(31.9%)	79	(68.1%)	Chi^2=21.583 p<0.001
B	102	6	(5.9%)	96	(94.1%)	

Table 5: Results of the analysis of the duration of pregnancy maintenance in Group A and B.

Group	n	Group		Relevance of differences
		x + SD	min-max	
A	117	13.7 + 10.1	1 – 29	p<0.001
B	105	7.3 + 5.6	1 – 22	

Table 6: Results of multidimensional regression with Klimek's scale as dependent variable.

Factor (independent variable)	Regression coefficient b	Standard error of regression coefficient b	p
Gestation period on admission	0.589	0.01	<0.001
Duration of pregnancy maintenance	0.143	0.024	<0.001
Gestational week of the beginning of the treatment by a doctor	–0.101	0.042	<0.01

Table 7: Results of multidimensional regression with duration of pregnancy maintenance as dependent variable.

Factor (independent variable)	Regression coefficient b	Standard error of regression coefficient b	p
Duration of antibiotic application	0.314	0.068	<0.001
Gestational week of the beginning of health care	–0.226	0.066	<0.001
Gestational period on admission	0.098	0.070	0.53 (NS)

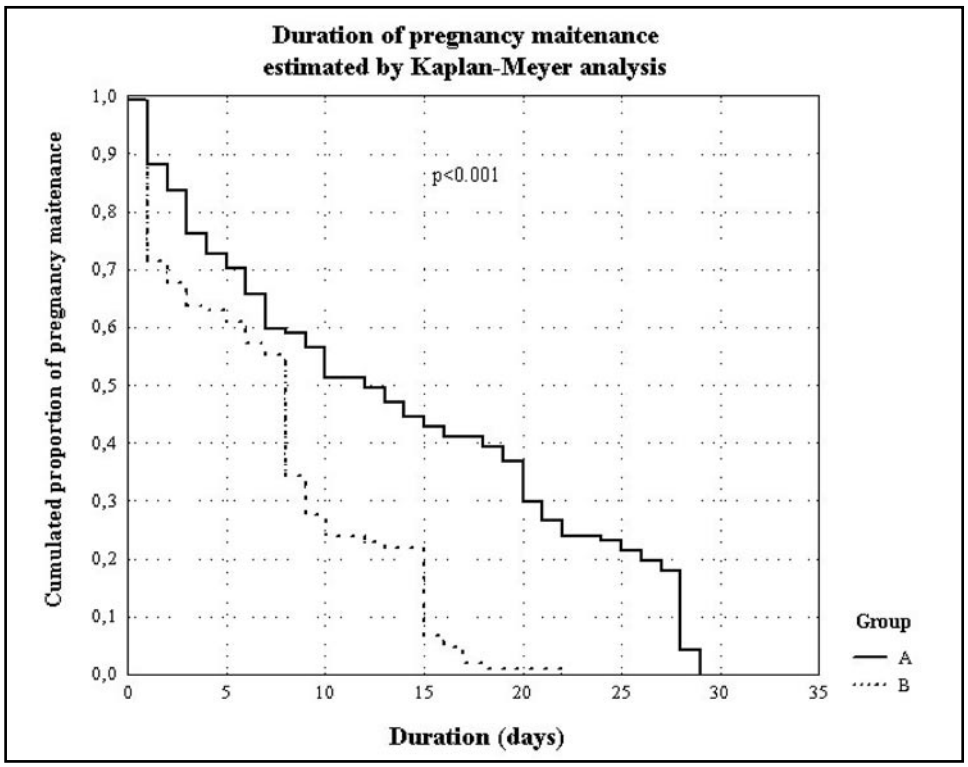

Figure 1. Duration of pregnancy maintenance estimated by Kaplan Meyer analysis

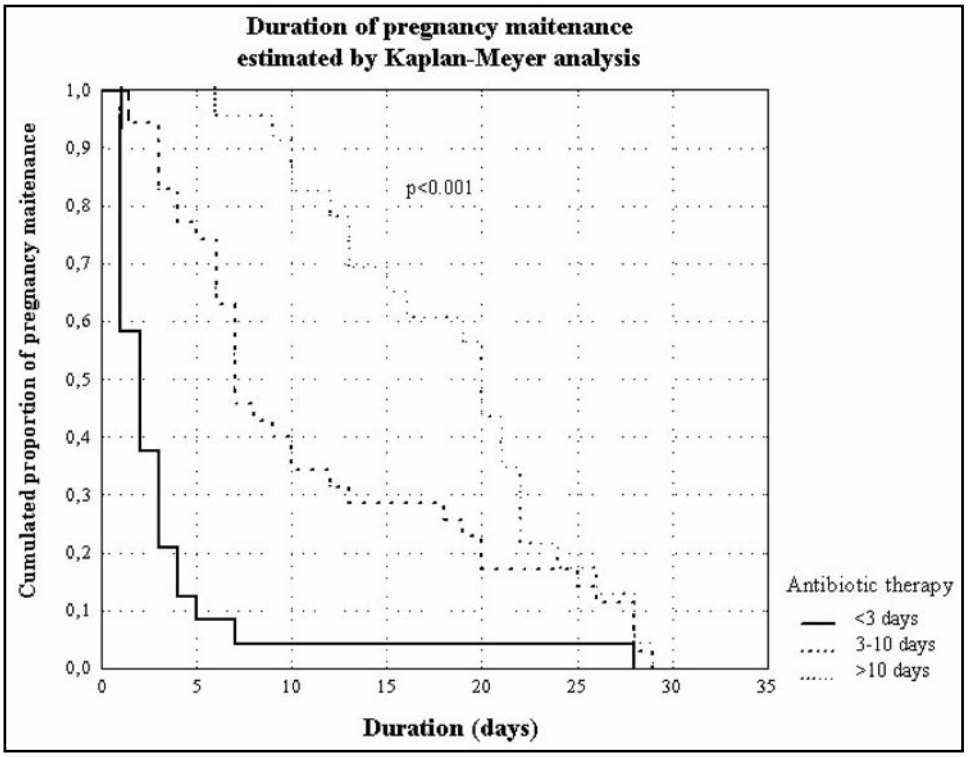

Figure 2. Effect of the pregnancy maintenance treatment estimated by Kaplan-Meyer analysis in correlation with the duration of the application of antibiotic treatment.

Comparison of the pregnancy maintenance duration estimated by Kaplan-Meyer analysis of cumulated time curves has proved the level of significance ($p<0.001$), Fig. 1. During the whole observation period, the curve of pregnancy maintenance for Group B ran significantly lower than the curve calculated for Group A. In Group B, in 60% of cases delivery took place on the sixth day, whereas in Group A, in 60% of cases delivery took place in the ninth day of treatment. During further observation one notices a quick slump of the curve in Group B, which terminates in the twenty-second day of treatment when all the patients had already delivered. In Group A the slump of the curve is slower, and the last labour took place on the twenty-ninth day of treatment.

Figure 2 shows a noticeable correlation between the efficacy of tocolysis combined with antibiotic therapy and the duration of antibiotic application. The time of pregnancy maintenance in Group A depends on the time of the application of antibiotic treatment ($p<0.001$). This correlation was depicted by drawing the curves of cumulated proportion of pregnancy maintenance in the patients who were administered

antibiotic for 3 days, in the period from 3 to 10 days and more than 10 days.

There is a clear correlation between the assessment of the condition of neonates with the use of the APGAR scale, as well as between the estimate of natal maturity with the use of K-scale, and the time of pregnancy in a research group, with the exception that the assessment of a neonate by means of the K-scale shows greater dependence on the duration of pregnancy maintenance, so it can be used as a measurement of the influence of certain chosen parameters connected with the course of pregnancy on the condition of a neonate.

Such an assessment was conducted by calculating the analysis of multidimensional regression where the stage of neonate's maturity according to Klimek's scale was established as a dependent variable, whereas the time of pregnancy prolongation, the gestation period during the first visit and on admission were set as independent variables.

Adjustment of the model was received at the level of significance $p<0.001$, which means that at least one of the independent variables established within the model significantly influences the stage of neonate's maturity assessed according to Klimek's scale.

In Table 6, results of multidimensional regression were presented. Regression coefficient b was established as slumping. It offers a possibility of rating the influence of factors analysed on a neonate's condition.

Significance of the influence of a given factor on dependent variable (the stage of neonate's maturity according to Klimek's scale) was also established.

The conducted analysis of multidimensional regression indicates that all the factors included in the analysis significantly influence the stage of neonate's maturity estimated by Klimek's scale. Gestation period on admission is the main factor, followed by the duration of pregnancy maintenance, followed by the gestational week at the beginning of the treatment. It is the inversely proportional influence. The later the care began, the worse a neonate's condition.

Analysis of multidimensional regression with the duration of pregnancy maintenance as dependent variable and the duration of antibiotic application (0 when antibiotic treatment was not administered), gestation period during the first visit, gestation period on admission as independent variables was also conducted. Adjustment of the model reaches the level of significance $p<0.001$, which means that the duration of pregnancy maintenance is significantly influenced at least by one independent variable within the model.

In Table 7, results of multidimensional regression were presented. Regression coefficient b was rated as slumping. This offers a possibility of rating the influence of analysed factors on the duration of pregnancy maintenance.

Significance of the influence of a given factor on dependent variable (duration of pregnancy maintenance) was also established.

The conducted analysis of multidimensional regression indicates that gestation period of a patient at the beginning of hospitalization significantly influences the duration of pregnancy maintenance (inversely proportional influence: the later a patient is taken care of by a doctor, the shorter is the time of pregnancy maintenance). However, the main factor influencing the duration of pregnancy maintenance is the duration of antibiotic treatment (inversely proportional correlation). Prolongation of antibiotic treatment duration influences the time of pregnancy maintenance in an inversely proportional way, which means that it positively influences the efficacy of tocolysis.

As can be concluded from the research conducted, the patients in Group A with the symptoms of imminent preterm birth were admitted to hospital almost three weeks earlier on average than the patients in Group B. And although the pregnancies in Group A lasted for about two weeks shorter than in Group B, this was a result of later admission of the patients in Group B to hospital. Application of antibiotic treatment as adjunctive treatment in tocolysis in Group A helped to prolong a pregnancy for over two weeks, whereas in Group B prolonging time amounted to 7.3 days on average. These differences reach the level of significance. It can be then recognized that in many cases of subclinical intrauterine infection administration of antibiotics along with tocolysis in the case of premature contractile activity of uterus could prolong the time of pregnancy and enable a neonate to develop abilities to survive outside maternal womb.

When comparing the results of the research with the literature, it can be concluded that the duration of pregnancy maintenance significantly depends on the duration of antibiotic treatment duration (Graph 2). In over a half cases of the patients who were administered antibiotics for more than ten days, pregnancy was successfully prolonged for about twenty days. This effect may be accounted for by the fact of applying therapeutically appropriate drug to fight the pathogens inducing infections. Thus the practice of introducing tocolysis assisted by broad-spectrum antibiotic treatment in cases where there are no microbiological investigations is undoubtedly justified. It seems that this model of clinical activity may result in significant improvements in prevention of preterm labours.

In Group A, more than one third of the pregnant women suffered from premature flow of amniotic fluid, whereas in Group B such complication occurred only in six cases. Despite more frequent incidence of this serious threat to preterm labour, tocolysis was applied for a statistically longer period in Group A than in Group B. This seems to be an appropriate place to formulate a thesis that this advantageous phenomenon could result from simultaneous application of antibiotic.

However, studies concerned with the efficacy of antibiotic treatment in the case of imminent preterm labour provide contradictory data [7,8,9,16,36,43]. It is believed that since one of the reasons of preterm labour is the infection of chorion and decidua, application of antibiotic therapy as a way of treating or assisting treatment of imminent preterm delivery may be a natural consequence of this etiology [7,8,9,16,36,43]. Antibiotic therapy administered simultaneously with

tocolysis in cases of imminent preterm labour induced by intrauterine infection may in many cases enable prolongation of pregnancy till a neonate matures enough to survive outside maternal womb and, in this way, it helps to decrease the number of complications resulting from prematurity. Antibiotic treatment should be applied according to existing procedures in cases of suspicion of ascending infection or suspicion of subclinical intrauterine infection, as well as in cases of clinical symptoms of foetus infection.

On the basis of the above-presented results of own research, which may supplement extensive literature on the subject, it can be concluded that antibiotic treatment enhances the efficacy of tocolysis, influencing the time of prolonging pregnancy in imminent preterm delivery. This synergistic effect is clinically crucial as in this way significantly larger number of children will be born at term and also a number of premature neonates who survive may be increased.

Conclusions

1) Antibiotic treatment administered simultaneously with tocolysis in threatened pregnancy enhances the efficacy of tocolytic treatment.
2) The efficacy of antibiotic treatment depends on the time of its application.
3) Out of three currently applied criteria of pregnancy maintenance, the most useful for estimating gestation period is the criterion of neonate's maturity.

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