

The particularities of placental morphogenesis within pregnant women, suffering from lung tuberculosis (結核合併妊娠における胎盤の形態学的特徴)

S Hirota¹⁾ A.V.Yakimova²⁾ A.P.Nadeev³⁾ V.A.Shkurupiy⁴⁾

要旨：結核は世界的に蔓延している感染症であり、患者数は2003年時にはロシア、日本、チェコの順である。更に深刻な問題として若年者に発症が多く、それゆえ妊婦が結核に感染し未治療のケースが多い。妊娠時における胎盤の虚血性変化は妊娠中毒症よりも結核に罹患した場合の方が強く、未治療の方が更に強い。これは胎盤の絨毛への血流障害、血管新生の障害が原因である。結核合併妊娠時に抗結核薬投与によって胎盤の虚血が改善される傾向にある。この度、病理組織学的見地からも抗結核薬による早期治療が胎盤の虚血改善に重要であると考えられた。

キーワード：結核、妊娠、ロシア

Summary : Tuberculosis is among the most wide-spread infectious diseases in the world. Patient number of tuberculosis is first Russia, second Japan, and third Czechoslovakia at 2003. Recently, as an important problem, patients of younger people are increasing. So, there are many pregnancies who are tuberculosis with no medication. Placental insufficiency is appeared stronger in tuberculosis than in toxemia. In cases of tuberculosis, compensation of placental insufficiency is realized by cellular and mixed mechanism of adaptation. It is characterized by three-dimensional density reduction of cytotrophoblast in contrast with pregnancies suffering from toxemia of pregnancy and in healthy pregnancies. Which follows that the most expressing pathomorphologic changes were in the placentas from patients suffered from active tuberculosis, who hadn't been treated during their pregnancy. The mechanism of the placental insufficiency origin is mainly concluded in breach vilii vascularisation and breach of the placental angiogenesis. So, we should treat pregnant women with medication who are suffering from lung tuberculosis immediately.

Key words : Tuberculosis, Pregnancy, Russia

[Introduction]

Tuberculosis is among the most wide-spread infectious diseases in the world. Patient number of tuberculosis is first Russia, second Japan, and third Czechoslovakia at 2003. In the arena of contagious diseases, tuberculosis occupies the second leading reason to deaths. 2 million people die from tuberculosis annually in developing countries and in a determined area of the industrial developed countries. Frequently tuberculosis is the most high among women and men at their reproductive age¹⁾. In Russian Federation beside women exist: rising morbidity by tuberculosis at age 20-35 years, moreover 35 % of all cases happen at this age, including - for 20-28 years - about 20 % all revealed sick, and the growing of morbidity at age from 20 to 57 years, begun after 1998²⁾. Novosibirsk is found nearly in zone of the epidemics of the tuberculosis: disease for nine months 2005 has formed 92.6 cases on population of 100 thousands¹⁾. Researching tuberculosis as reason of the obstetric complications, many authors point to increasing of the frequency of the complications of pregnancy and sort such as EPH-gestosis (edema, proteinuria, hypertension) incompetent pregnancy, preterm rupture of the water bag, anaemia. Point to intercoupling the frequency intrauterine hypoxia of fetus, prenatal mortality and innate vice of the development (in particular, spina bifida) with the form and phase of the maternal tuberculosis³⁻⁵⁾. Considering aforesaid, problem of the combination to pregnancy and tuberculosis is in present time more actual. The purpose

1) 日本赤十字秋田短期大学教授 2) Russia州立Novosibirsk大学准教授 3) 同講師 4) 同教授

of this research is to study the particularities of placental morphogenesis within pregnant women, suffering from tuberculosis, with a provision for natural pathological processes and conducted treatment.

[Material and Methods]

From 2001 to 2006, 108 pregnant women age from 20 years old to 27 years old were examined at gestational age 37-40 weeks in Novosibirsk State University Hospital, 48 of whom had active tuberculosis. For undertaking the morphological study of the afterbirth, on criterion of presence or absences of therapy by tuberculostatic medicines during pregnancy, were chosen following groups of pregnant: Group I (25 cases), who were suffering from tuberculosis of the respiratory system, got antibiotic therapy during pregnancy. Group II (23 cases), who were suffering from tuberculosis of the respiratory system, didn't get therapy by tuberculostatic medicines during pregnancy. The most often complication to pregnancy in both group was EPH-gestosis, for this reason as groups of the comparison: Group III (40 cases), who were taken pregnant with EPH-gestosis and no suffered from tuberculosis. Group IV (20 cases), who were taken pregnant with no EPH-gestosis and with no tuberculosis. Beside all examined pregnant age did not exceed 27 years: Group I (25 cases), pregnant average age has formed 23.4 ± 1.1 years, Group II (23 cases) was 26.02 ± 0.6 years. In control groups, Group III (40 cases) was 25.6 ± 0.3 and Group IV (20 cases) was 23.2 ± 0.3 accordingly. Beside majority pregnant tuberculosis was diagnosed before pregnancy 29 cases (60.42%), during pregnancy 19 cases (39.58%). Distribution of patients by the forms of the tuberculosis is presented in table 1.

The morphological study afterbirths of said groups were organized. For the microscopy, the material was fixed in 10% solution of neutral formalin with the following potting in paraffin. Histological probes painted by hematoxylin and eosin with the following undertaking overview light microscopy and morphometry. Counted three-dimensional density (Vv) of terminal villi in placenta, three-dimensional density of trophoblast, connective tissue, vessels of terminal villi, as well as three-dimensional density subtrophoblastic, axial, paracentral capillars, syncytiocapillar membrans of terminal villus, symplastic nodules, intervilli spaces and intervilli maternal fibrinoid. The digital material was subjected to the statistic processing, validity difference between average value measured parameter defined by means of Student-t. Reliable considered the differences if $p < 0.05$.

[Results]

As follows from table 1, most often existed infiltrative and focal lung tuberculosis: 23 cases (47.9%) and 9 cases (18.7%) pregnant accordingly, from all examined 14 cases (29.2%) pregnant were BK positive (Group I, II). Beside 19 cases (39.5%) of the women, tuberculosis was diagnosed for the first time during persisting pregnancy. Before approach persisting pregnancy in 21 cases (43.7%) of the women and in 8 cases (16.8%) of the women was noted relapse of the tuberculosis (Group I, II). The intensification of the tuberculosis process in lungs was expressed in transition from less active phase to more active. At analysis of the currency of pregnancy in women suffered from tuberculosis, we paid attention to such complication of pregnancy as EPH-gestosis. Only 5 cases pregnant, suffered from tuberculosis, didn't have such complication during pregnancy. Mainly - in 43.7% cases - a degree to this complication was average, in 36.6% cases - light and only in 19.7% examined this complication of pregnancy was absent.

Pregnancy finished at gestational age: 38.0 ± 0.6 weeks in Group I and 37.1 ± 0.6 weeks in Group II. On this factor, Group I, II realistically did not differ from Group III, where labor has occurred at gestational age 38.1 ± 1.0 weeks. Notable that there was the reliable difference with group of "healthy pregnant" Group IV: in this group delivery have occurred at gestational age 39.9 ± 0.8 weeks. Thereby, called on observations are indicative of the fact, that among pregnant suffered from tuberculosis, birth occur realistically earlier than beside healthy pregnant at the average for 2 weeks without any dependence from the form of the tuberculosis.

The average mass of the afterbirth in Group I existed pregnant was 487 ± 13.04 g, in Group II was 442 ± 10.6 g, in Group III was 495.1 ± 14.1 g, but in Group IV was 518.1 ± 15.1 . Reliable differences were on mass of

the afterbirth in Group I, II from other groups. In Group I, II mass afterbirth also was realistically less than in Group III, IV ($p < 0.05$).

The clinical manifestations of placental insufficiency viewed in fetal hypotrophy (the mass-height factor less than 60) were revealed: in Group I, II 22 cases (45.8%) - 8 cases in Group I and 14 cases in Group II. In Group III, newborns with mass-height factor less than 60 were 14 cases (35%), and in Group IV such newborn was only 1 case (5%). The differences were reliable between Group IV and rest ($p < 0.05$). The average body length of the newborns in Group II has formed 48 ± 1.4 cm and it realistically was less than in newborns from other groups ($p < 0.05$): 52.2 ± 0.0 cm - in Group I, 50.3 ± 1.9 cm - in Group III, 52.1 ± 1.8 - in Group IV.

Under morphological study of the afterbirth, signs of chronic placental insufficiency were revealed in almost all patients in Group I, II and Group III. The typical particularity for groups of the women suffered from tuberculosis (Group I, II) was presence pathological placenta unripeness in version of intermediate differentiated villi, such variant was diagnosed in each fifth case that realistically did not differ from result of the study of the afterbirth in Group III. In Group IV, such variant wasn't met. Also in most cases: 18 cases (72.0%) in Group I and 15 cases (65.2%) in Group II were diagnosed as variant of dissociated development of cotyledones and the similar situation was 31 cases (78.1%) in Group III. In Group IV, variant of dissociated development of cotyledones was met in 40% cases only. The mature type of the placenta was diagnosed in two times less beside patients in Group II, in contrast with Group I; though necessary to notice that difference data between Group I and Group II are not reliable. In Group III, mature type of placenta wasn't diagnosed in any case. In detail results of afterbirth histological studies were provided in table 2.

In Group I, compensated nature of placental insufficiency was diagnosed in most of the observations. In Group II, chronic placental insufficiency nearly in half of the cases was compensated (beside 48% observations). In both specified group dominated the cellular mechanism of adaptation: in Group I - in 68.0%, in Group II - in 78.3% cases. In both group vascular type to adaptation, the most seldom was noted - from 8.7% in Group II to 12.0% in Group I. In Group III, compensated nature of placental insufficiency was diagnosed in 60.0% observations, sub-compensated in 35.0%. Herewith in half of the cases, compensation was realized by the cellular mechanism of adaptation, in 40% - by mixed, vascular type as well as in Group I, II was rare - 7.5%. In Group IV, morphological signs of placental insufficiency were diagnosed in 80% cases, however compensated nature was noted in 75% pregnant and only in 1 case (5.0%) existed sub-compensated chronic placental insufficiency. The cases sharing of the observation placental insufficiency by degree of the compensations is shown in table 3, types to adaptation are presented in table 4.

Morphological change conditioned shaping sub-compensate, decompensate placental insufficiency were presented in Group I, II in the manner of chronic frustration uterine-placental circulation (the chronic hemorrhagic attacks, stratifying hemorrhages in basal plate), significant degree of fibrinoid deposit in supchorial zone, intervillous maternal fibrinoid (three-dimensional density in Group I and Group II has formed 36.0 ± 0.8 % and 45.8 ± 0.6 % accordingly and has had a reliable differences as inwardly groups pregnant suffered from tuberculosis, so and between group of the comparison, $p < 0.05$) with area non-functional immured villus in combination with breach of the maturation villi tree on type intermediate differentiated and non-differentiated villus. The processes to adaptation were sparingly denominated (the centers of cytotrophoblast proliferation in intervillous space and symplastic nodules of terminal villus) and had had a focal nature. In Group III, three-dimensional density intervillous maternal fibrinoid with non-functional immured villis at the average formed 38.8% placental issue. In Group IV, frustration of uterine-placental circulation was absent, but three-dimensional density intervillous maternal fibrinoid has formed 29.6 ± 0.8 %. As it can be seen from table 5. Predominating in Group I, II, III, type to adaptation - cellular was not typical for placentas of Group IV (in them adaptive processes were presented by terminal villus hyperplasia, dilatation and plethora of terminal villus capillaries, shaping of syncytiocapillary membranes)⁴⁾. There are reliable differences on type of the adaptation from Group IV to the others. Group I, II realistically did not differ neither on degree of the compensations, nor on its mechanism. Then between Group I, II

and Group III, there is reliable difference on frequency of the mixed type to compensations. The most interesting results we received by morphometry of placental tissue.

At study of three-dimensional density of terminal villus in placentas reliable difference was discovered between group women suffered from lung tuberculosis (Group I, II) and group of the women with EPH-gestosis (Group III), and between Group I, II and Group IV: three-dimensional density of terminal villus in Group I and Group II has formed $56.0 \pm 1.8\%$ and $52.01 \pm 2.01\%$ accordingly. In group pregnant with EPH-gestosis (Group III), this parameter has formed $81.2 \pm 1.5\%$, but in Group IV reached $98.6 \pm 1.6\%$, ($p < 0.05$). At study of three-dimensional density of cytotrophoblast and symplastic nodules of terminal villies were the reliable difference between Group I, II and Group III; group of women suffered from tuberculosis and group pregnant with EPH-gestosis: three-dimensional cytotrophoblast density in Group I and Group II has formed $23.4 \pm 1.8\%$ and $21.1 \pm 1.9\%$ accordingly then in Group IV, this factor reached $27.6 \pm 0.8\%$, but in Group III - $22.2 \pm 1.2\%$ ($p < 0.05$). Three-dimensional density of non-vascular terminal villus was highest in group patients, suffered from tuberculosis and not got corresponding to treatments (Group II): $15.0 \pm 1.2\%$. In Group I, this factor has formed $7.2 \pm 1.0\%$, but in Group III - $9.5 \pm 0.5\%$. The least three-dimensional density of non-vascular terminal villus was in placentas in Group IV - $4.7 \pm 0.6\%$. In detail results histological studies of terminal villies, cytotrophoblast, symplastic nodules are shown below in table 5.

The reliable difference among groups were received at study of three-dimensional density acsial capillary of terminal villies: the least density is noted in Group III - $10.4 \pm 0.5\%$. Beside Group I, II, three-dimensional density acsial capillary of terminal villies was realistically low in contrast with Group IV too: in Group I - $11.02 \pm 1.7\%$, in Group II - 10.1 ± 0.8 . In Group IV, this factor reached $14.0 \pm 1.2\%$. Three-dimensional density of paracentral capillaries also realistically differed among groups ($p < 0.05$): in Group IV, it was $15.0 \pm 1.2\%$, it was the least in Group III - 14.8 ± 1.2 , in Group I - 21.9 ± 1.1 and in Group II - $29.0 \pm 1.0\%$. Three-dimensional density of subtrophoblastical capillaries in Group IV was $50.2 \pm 0.8\%$. Three-dimensional density of sub-trophoblastical capillaries in Group III was realistically different from the same factor in Group IV - it was the most low among all groups ($43.6 \pm 1.2\%$), also reliable difference between the Group IV and Group I, II ($p < 0.05$): in Group I this $47.1 \pm 1.6\%$, in Group II $44.0 \pm 1.1\%$. Three-dimensional density of terminal villus with sincytiocapillary membranes realistically differed ($p < 0.05$) from Group IV in contrast with Group I, II, III. High relative density of terminal villus with sincytiocapillary membranes was noted in Group IV - in $56.2 \pm 0.8\%$, in Group I, this fact was determined in $22.1 \pm 1.8\%$ cases, in Group II - in $23.5 \pm 0.8\%$, in Group III - in $32.4 \pm 1.0\%$. In placenta of patients sick with tuberculosis visually one finds either large centers of caseous necrosis, or plural milliar centers on surface of the placenta, in villiar chorion and fetal membranes. As a rule, infect of placenta occurs by hematogenic way, less - from the focus of the infection in endometrium. By histological study in miscellaneous organ area small or more large focus of caseous necrosis, surrounded by non-specific cellular reaction comes to light. In intervilli space the concourses of the polymorphic cells and fibrin are revealed, which sometimes are subjected to the caseous necrosis. In adjoining to such area in villus diffuse growing of specific granulation tissue and tuberculosis tubercles appear. Quite often in villi vessels blood clods are formed or bright spot obliteration occurs. If the infection spreads from focus in endometrium, the similar changes can come to light in membranes of the afterbirth⁶⁻⁷) As a result of our studies, inflammatory change in the afterbirths of patients, suffered from tuberculosis, were discovered in all cases (100%). These changes were mainly presented in the manner of diffuse productive inflammation (100% observations). The reliable difference between Group I and Group II wasn't revealed. The Productive inflammation in decidua basalis was diagnosed in 18 cases (37.5%), in decidua parietalis - in 30 cases (62.5%), in chorion villus - in 12 cases (25.0%), in intervilli space - in 10 cases (20.8%) of the observations. Granulomatic basal deciduitis was diagnosed in 4 cases. The painting by Ziehl Neelsen method for the detection of mycobacterium tuberculosis didn't give the positive result. There was not any focus of the necrosis. In Group III also were an inflammatory changes, mainly in the manner of parietal deciduitis - 16 cases (40.0%), basal deciduitis was diagnosed in 10 cases (25.0%), acute villitis was diagnosed in 14 cases (35.0%), acute intervill-

litis we have found in 10 cases (25.0 %). In Group IV, inflammatory changes were of acute focal type, localized in decidual membrane (focal deciduitis) and were diagnosed in only 5 cases.

[Discussion]

Most often in pregnant women infiltrative and focal lung tuberculosis exists, in not less than 44.0 % of sick pregnant mycobacterium tuberculosis can be detected, by this reason they are presenting epidemiological danger for population. One of important problems is frequency intrauterine hypoxia of fetus³⁻⁵. The mass of the after-birth in patient with tuberculosis was realistically lower than in pregnant with EPH-gestosis and than in pregnant, not suffered from tuberculosis. So, continuous placental insufficiency is most dangerous state for fetal. The compensated placental insufficiency was revealed in 2/3 patients, who got treatment by anti tuberculosis remedies during pregnant and revealed only in half of pregnant who did not get such treatment. In cases of tuberculosis, the compensation of placental insufficiency is realized by cellular and mixed mechanism of adaptation. It is characteristic of three-dimensional density reduction of cytotrophoblast in contrast with pregnant suffered from EPH-gestosis and healthy pregnant. It may be said that one of important fears for placental growing is tuberculosis than EPH-gestosis.

Whole of aforesaid follows that at tuberculosis the most expressing pathomorphologic changes were in placentas from patients suffered from active tuberculosis, who hadn't been treated during pregnancy. And mechanism of the placental insufficiency origin is mainly concluded in breach villi vascularisation and breach of the placental angiogenesis. So, we should treat medications for pregnant women suffering from lung tuberculosis immediately. We have to make efforts to improve placental insufficiency and change to compensated state.

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Table 1

**Forms of the tuberculosis, diagnosed in two investigated groups of pregnant women
(in percent to number of pregnant women in each group)**

Forms of the tuberculosis	Group I (n=25)		Group II (n=23)	
		BK+		BK+
Infiltrative lung tuberculosis	13 (52.0 %)	5	10 (43.4%)	4
Focal lung tuberculosis	2 (8.0%)	0	7 (30.4 %)	1
Disseminated tuberculosis	1 (4.0%)	1	2 (8.7 %)	1
Fibrosis and Cavernosis lung tuberculosis	1 (4.0 %)	1	1 (4.3 %)	1
Lung tuberculoma	5 (20.0%)	0	1 (4.3 %)	0
Tuberculosis Pleurisy	2 (8.0 %)	0	1 (4.3 %)	0
Caseosis Pneumonia	1 (4.0 %)	0	1 (4.3 %)	0

Table 2

The results of afterbirth histological studies

Groups	Intermediate non-differentiated villi		Intermediate differentiated villi		Dissociated development of cotelidones		Mature type of the placenta	
	Number	%	Number	%	Number	%	Number	%
I n=25	5	20.0	0	0.0	18	72.0	2	8.0
II n=23	6		1	4.3	15	65.2	1	4.3
III n=40	8	20.0	1	2.5	31	77.5	0	0.0
IV n=20	0	0.0	0	0.0	8	40.0	12	60.0

Table 3

The cases sharing of the observation placental insufficiency by degree of the compensations

Group	Compensated		Sub compensated		Decompensated	
	Number	%	Number	%	Number	%
I n=25	18	72.0 *	6*	24.0*	1	4.0
II n=23	11	47.8*	10*	43.5*	2	8.7
III n=40	24	60.0*	14*	35.0*	2	5.0
IV n=20	19	95.0*	1*	5.0*	0	0.0

*- ($p < 0,05$).

Table 4

Adaptation types in cases of placental insufficiency

Group	Cellular		Mixed		Vascular	
	Number	%	Number	%	Number	%
I n=25	17	68.0	5	20	3	12.0
II n=23	18	78.3	3	13.1	2	8.6
III n=40	21	52.5	16	40	3	7.5
IV n=20	3	15.0	10	50	7	35.0

Table 5

Three-dimensional density (Vv) of terminal villies, cytotrophoblast, symplastic nodules, non-vascular terminal villies in placentas of four investigated groups (M ± m).

Group	Terminal villies	Cytotrophoblast of terminal villies	Symplastic nodules of terminal villies	Non-vascular terminal villies
I n=25	56.0 ± 1.8 [#]	23.4 ± 1.8 [#]	57.5 ± 1.3 ^{*^#}	7.2 ± 1.0 ^{*^#}
II n=23	52.01 ± 2.1 [#]	21.1 ± 1.9 [#]	54.1 ± 2.0 ^{*^#}	15.0 ± 1.2 [#]
III n=40	81.2 ± 1.5	22.2 ± 1.2	60.7 ± 1.8	9.5 ± 0.5
IV n=20	98.6 ± 1.6	27.6 ± 0.8	44.8 ± 1.1	4.7 ± 0.6

Explanation: # – veritable difference among data for I and II group and control group data;

[^] - veritable difference among data for I and II group and III group data;

*- veritable difference between data of I and II group.