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MELANOMA OF THE SKIN AND PREGNANCY

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ABSTRACT

The effect of pregnancy on the clinical course and prognosis in melanomas is the subject of contradictory observations and conclusions. There are known data on the effect of certain hormones on the pigment system and the relationship between sex hormones and malignant melanoma. It was found that there are special receptors for estrogens in the cytoplasm of primary melanoma cells (Bruli S., 2010). In the United States, it is possible to determine to what extent this is the case (Sadoff L. and others, 2013; Lerner L. et al., 2019). However, A.Adam. (2011) did not find a link between the use of hormonal contraceptives and the occurrence of melanoma. To.Sutherland. (2013) indicate an increase in hormone levels during pregnancy, and then a rapid decrease after childbirth.

It is quite obvious that a change in the hormonal status associated with pregnancy causes the activation of human pigment nevi (Nivinskaya M. M., 2010; Tucker Ltd.V. and co-author, 2010). Thus, observations are described, where it is indicated that during pregnancy there was an increase in the size of its congenital nevus and ulceration, and after childbirth or abortion, the nevus underwent reverse development (P Iconography.L. and coauthor, 2010; Riberti S. and coauthor, 2011). In the summer of the year, the first time in the summer of the year, the first time in the summer of the year, the first time in the summer of the year.S., 2013; Byrd B.P. and others., 2014; Stewart J., 2015; Kreisel Howe. and others., 2015; Allen.R., 2017; Natanson., 2016; Bork K. and others, 2015).

R.D. Ikonopisov and co-author. (2010) described observations of complete spontaneous regression of breast skin melanoma with metastases to the axillary and supraclavicular lymph nodes in a young woman who came after the successful completion of pregnancy.

Regarding the effect of pregnancy on the prognosis in women with melanoma of the skin, the opinion of researchers is contradictory. A., Haughton and co. (2011) conducted a detailed retrospective analysis of 12 pregnant and 175 unmarried women of childbearing age with skin melanoma, in which they noted a low three- and five-year survival rate (65% and 55%) in pregnant women compared with non-pregnant women (86% and 83%). The fact that



pregnancy adversely affects the course of melanoma is also indicated by other researchers (Ilyin I.A., 2019; Loboda I.D. and co-authors, 2010; Nivinskaya I.Sh., 2010; Landthaler M. et al., 2015). On the contrary, some authors believe that pregnancy has no effect on the prognosis for skin melanoma (Bohan Ya.V. and co., 2011; Shacker E.c. et al., 1958; George P.A. et al., 2010; White L.P. et al., 2011; Nathanson L. et al., 2017; Haßler N. et al., 2019; Reintgen D.s. et al., 2015; Holly E.A., 2016; Fiedler H. et al., 2016).

A number of researchers believe that when assessing the effect of pregnancy on the course and prognosis of skin melanoma, it is necessary to take into account the extent of the spread of the tumor process. A.P. Shanin (2017) indicates that, on the one hand, with local melanoma, pregnancy does not affect 5- and 10-year survival; on the other hand, in the presence of regional metastases it clearly leads to the dissemination of the process. E.G.Jung (2019) pointed out that pregnancy with local melanoma of the first clinical stage does not worsen the prognosis, at the stage of the disease negatively affects the prognosis, at the second stage it can spread to the fetus. According to the author, the five-year survival rate at stage I is from 50 to 90%, at stage I - 10-20a, at stage I - 5%. M.N.shin et al. (2016) also revealed that pregnancy at stage I worsens the prognosis of the disease. There is evidence that early pregnancy does not affect the prognosis of the disease, and when combined with melanoma and pregnancy in late terms, the prognosis worsens (Smith R.S., Randall P., 2019).

Regarding the preservation of pregnancy in women with melanoma of the skin, the opinions of researchers are contradictory. According to I.D.Loboda et al. (2010), termination of pregnancy in both early and late terms does not improve the clinical course of melanoma. However, the authors suggest that therapeutic abortion in the late stages of pregnancy will significantly accelerate the process of metastasis, in connection with which they will renege the preservation of pregnancy in the late stages. c.01aen (2017) also does not consider termination of pregnancy absolutely indicated in all cases. E.G.Jung (2019), N.Fiedler et al. ((2016) indicates that the issue of maintaining pregnancy in the first clinical stage should be decided individually. When regional metastases, pregnancy significantly worsens the prognosis, and therefore must necessarily be interrupted. At the same time Nevinskaya et al. ((2012) indicate that neither the role nor abortions were given to the progressive treatment of melanoma when she arose against the background of pregnancy.

Taking into account the great interest in this problem and the ambiguities in a number of cases concerning the melanoma tech during pregnancy, we decided to retrospectively analyze the medical histories of 102 pregnant women suffering from skin cancer who were examined and treated in the Second World War of the USSR Academy of Sciences from 2010 to 2014, inclusive, which in general amounted to 5 of all 2018 melanoma patients women who were treated during this period. The 3-, 5- and 10-year survival rate among this group of 102 pregnant women was compared in terms of survival with a group of 42 women with skin melanoma during lactation, and a group of 599 women with childbearing age, with normal menstrual cycles, who did not have pregnancy during the disease (control group).

The diagnosis in all patients was confirmed by histological examination data. All groups of patients when compared by age, localization of the primary tumor, the level of invasion and thickness of the tumor were similar.

The distribution of pregnant women with skin melanoma by age was as follows: under 19 years - 3 (3%), from 20 to 29 years - 55 (54%), from 30 to 39 years - 40 (39%), 40 years and older - 4 (4%). The youngest woman was 18 years old, the oldest was 43 years old. The average age of the patients was 28.7+0.6 years. The youngest woman in the control group was 18 years old, the oldest was 40 years old. The average age in this group was 32.0+0.2 years.

Table 1. Distribution of pregnant women and control group patients depending on the location of the primary tumor.

Tumor localization	Pregnant women		Control group	
	abc	%	abc	%
Head, neck	15	14,7	68	11,3
Body	34	33,3	194	32,2
Upper limbs	5	4,9	70	11,7
Lower Limbs	48	47,1	267	44,6
total	102	100	599	100

It should be noted that, as usual in jenshin with whole skin, in pregnant women, the tumor was most often localized on the lower extremities and the tulovishe. In the group of pregnant women with melanoma, the tumor was primary-multiple, and both tumors were dolocalized on the lower limb.

During histological examination of the drugs, nodular melanoma was most common (79,13). The level of invasion of Tumor cells by Y.Dark was detected in 4 pregnant women out of 131 patients in the control group. The thickness of the Breslow tumor was determined in 32 pregnant women and 129 patients of the control group.

Table2. Distribution of wooden women and control group patients depending on the level of invasion and tumor thickness (3 mm)

Morphological signs	Pregnant women		Control group	
	abc	%	abc	%
The level of invasion				
I	0	0	1	0,8
II	3	6,8	13	9,9
III	20	45,5	55	2
IV	15	34,1	51	38,9
V	6	13,6	11	8,4
The thickness of the tumor in mm				
0,74	1	3,1	4	3,1
0,75-1,49	5	15,7	27	20,9
1,50-2,99	9	28,1	41	31,8
3,00-4,99	8	25	34	26,4
5,00 и более	9	28,1	23	17,8



From the table. It can be seen that, both in pregnant women and in the control group, 2,1,0 Levels of invasion were most common (79.5% 80.9%, respectively), as well as in infants, tumors with a thickness of more than 1.5 ml prevailed in the control group — 81.1% and 76%.

Upon admission to treatment in 82 (80.4%) pregnant women and 477 (79.6%) patients of the control group, the process was local (I clinical stage). In 13 (12.7%) pregnant women and 91 (15.2%) patients of the control group, the process was local-regional (stage II). And 7 (6.9%) pregnant women, and 31 (5.2%) patients of the control group already had distant metastases (stage III).

To study the effect of pregnancy on the prognosis for skin melanoma, as mentioned above, we conducted a survival analysis of 102 women who had melanoma during pregnancy, and 599 women of childbearing age who did not have pregnancy during the melanoma disease (control group).

Table 3. Survival of patients with melanoma of the skin depending on the duration of pregnancy and on the clinical stage of the disease

A group of patients	Clin. Disease stage	The number of patientsx (%)	Survival rate %			Median of survival rate (months)
			3 yrs	5 yrs	10 yrs	
Pregnants	I	82(80,4)	65,2±5,8	44,4±6,7	26,0±7,4	55,0±8,2
	II	13(12,7)	37,0±14,6	37,0±14,6	-	20,6±4,3
	III	7(6,9)	-	-	-	7,0±2,6
Control	I	477(79,6)	70,9±2,2	53,6±2,6	43,0±2,8	69,8±11,2
	II	91(15,2)	29,6±5,0	23,6±4,8	17,9±4,6	23,3±3,1
	III	31(5,2)	5,6±4,4	5,6±4,2	-	8,3±1,5
Pregnants	All stages	102(100)	57,0±5,3	37,7±6,9	22,0±6,3	48,8±8,7
Control		599(100)	61,0±2,1	46,4±2,3	36,8±2,4	49,6±10,2

All 102 pregnant women with melanoma skin, depending on the duration of pregnancy, were divided into 2 groups:

- 1) 76 (74.5%) patients whose clinical manifestations of melanoma occurred in the 1st half of pregnancy;
- 2) 26 (25.5%) patients who had melanoma in the 2nd half of pregnancy.

We analyzed the survival of women with melanoma in the 1st and 2nd half of pregnancy by stages and compared these results with the survival of patients in the control group and in the group where melanoma occurred during lactation. The results of these studies are presented in the table. . As can be seen from the table, survival in all stages in patients with skin melanoma in the 1st half of pregnancy and during lactation was higher than in patients in the 2nd half of pregnancy, but the differences were not statistically significant. It can also be noted that the survival rates at the first clinical stage in the 1st half of pregnancy did not differ significantly from those of patients in the control group, and in the 2nd half of pregnancy,



significantly low 5- and 10-year survival was revealed compared with non-pregnant women with melanoma in the control group.

Thus, the results of our studies showed that in all stages of skin melanoma, survival was lower in the 2nd half of pregnancy compared to the 1st half and lactation period. The survival rate of patients with clinical stage T in the 1st half of pregnancy did not differ significantly from that in the control group, and in the 2nd half of pregnancy had a significantly low 5 - and 10-year survival rate. Consequently, low survival rates in patients with stage t skin melanoma should be attributed to those women whose melanoma manifested in the 2nd half of pregnancy. It is possible that the high level of estrogens and somatotropin observed during this period of pregnancy is important, and the effect of these hormones is manifested in stimulation and proliferation, including tumor.

Out of 102 pregnant women with melanoma of the skin, we could not find out the fate of the last pregnancy in only 2 patients. Out of 100 patients, pregnancy was preserved in 60 and terminated in 40. in the 1st half, pregnancy was preserved in 36 and terminated in 39, and in the second half, pregnancy was preserved in 2+ and terminated in only one patient who died 42 months later. from melanoma metastases to the brain. The analysis of survival depending on the termination of pregnancy in the 1st and 2nd half of it, as well as in general, regardless of the duration of pregnancy, is presented in the table and in Fig. It should be noted that in the 1st half of pregnancy in the group of patients where the severity was preserved, the survival rate was higher compared to patients who had an abortion, but statistically significant differences occurred only when assessing 5-year survival, which was 56.5% and 28%, respectively ($p < 0.05$). In general, regardless of the duration of pregnancy, the 5- and 10-year survival and median were higher in all women with melanoma who had their pregnancy preserved compared to those who had their pregnancy terminated, but the differences between them were statistically unreliable.

Table 5. The survival rate of patients with melanoma of the skin, depending on the duration of pregnancy and its temporary interruption, as well as in general, regardless of the duration of pregnancy.

Clinical signs	Termination of pregnancy was +, was not -	Number of patients	Survival rate%			Median of survival rate (months)
			3 yrs	5 yrs	10yrs	
1 half of pregnancy	+	36	66,0±8,8	55,5±9,7	39,5±11,3	68,3±18,3
	-	39	56,4±8,5	28,0±9,5	18,6±9,9	42,6±13,5
2 half of pregnancy	+	24	38,7±11,0	19,3±11,1	9,6±8,8	29,8±8,1
	-	1	100±0,0	-	-	42,0±6,0
All pregnant	-	60	54,8±7,1	41,6±7,1	22,6±8,1	52,7±11,6
	+	40	57,7±8,4	26,7±9,2	17,8±9,5	42,2±10,8



We also analyzed the survival rate of pregnant women with melanoma, depending on the clinical stage, the duration of pregnancy and the time of its termination.

Table 6. Survival of patients with melanoma of the skin depending on the duration of pregnancy the stage of the disease and termination of pregnancy

Group of patients	Clinical stage of disease	Termination of pregnancy was +, was not -	Number of patients x	Survival %			Median of survival rate (months)
				3 yrs	5 yrs	10 yrs	
1 half of pregnancy	I	+	31	72,1±9,0	66,5±9,9	45,4±12,7	90,5±25,3
		-	29	67,8±9,4	33,3±11,2	22,2±11,7	49,9±10,6
	II	+	5	25,0±21,6	25,0±21,6	-	20,0±4,0
		-	6	42,4±22,0	42,4±22,0	-	19,7±16,3
	III	+	0	-	-	-	-
		-	4	-	-	-	8,0±4,0
2 half of pregnancy	I	+	20	46,6±12,4	23,3±13,2	11,6±10,5	34,5±6,8
		-	1	100±0,0	-	-	42,0±6,0
	II	+	-	-	-	-	18,6±6,0
		-	0	-	-	-	-
	III	+	3	-	-	-	6,0±3,4
		-	0	-	-	-	-
All pregnant	I	-	51	61,9±7,6	51,0±8,5	27,1±9,6	61,0±14,6
		+	30	69,1±1,0	31,6±10,8	21,1±11,2	48,4±11,0
	II	-	6	20,0±17,9	20,0±17,9	-	19,5±3,3
		+	6	42,4±22,0	42,4±22,0	-	19,7±16,3
	III	-	3	-	-	-	6,9±3,4
		+	4	-	-	-	8,0±4,0

It can be noted that at the I clinical stage in the 1st half of pregnancy, 3-, - and 10-year survival and its median were in those patients where pregnancy was preserved, compared with patients whose pregnancy was terminated, however, significant differences between them were revealed only when assessing 5-year survival, which it was 66.5% and 33.3%



respectively ($p < 0.05$). On the contrary, at the P clinical stage of the disease at the same time of pregnancy, the indicators of 3- and 5-year survival were higher in women who had an interruption of pregnancy compared with patients whose pregnancy was preserved; the differences are statistically significant. It was not possible to identify significant differences in survival in patients with the clinical stage of the disease due to the small number of observations in the compared groups.

From the table. it is also seen that in the study of survival, regardless of the duration of pregnancy, the indicators of 3-year survival of stage 1 were higher in patients who had an abortion. On the contrary, 5- and 10-year survival rates were higher in patients whose pregnancy was preserved, but all these differences turned out to be unreliable. There are also no significant differences 3- 1 5- the survival rate in the second stage, although the survival rate was higher in patients who had an abortion. At stage I, median survival rates were higher in patients who had an abortion compared to patients whose pregnancy was preserved, but again the differences turned out to be statistically unreliable. Based on these data, it can be assumed that termination of pregnancy at stage I in both the 1st and 2nd half of pregnancy does not change the progressive course of the disease.

Thus, the obtained results of the study indicate that pregnancy has an adverse effect on the prognosis for skin melanoma. A statistically significant low 10-year survival rate was revealed in pregnant women both with local melanoma and in general, regardless of the clinical stage ($P < 0.05$). The prognosis in pregnant women with melanoma largely depends on the timing of pregnancy and the clinical stage of the disease. Survival in the 1st half of pregnancy and lactation is higher than survival before the 2nd half of pregnancy. Survival rates at stage 1 in the 1st half of pregnancy do not differ significantly from those of the control group, and in the 2nd half of pregnancy have significantly low 5- and 10-year survival compared with non-pregnant women, patients with melanoma ($p < 0.05$).

Interruption of pregnancy in its 1st half in patients with melanoma in stage I worsens, and in stage II improves the prognosis of the disease. A statistically significant 5-year survival rate was observed in patients in the 1st half of pregnancy at the melanoma stage, for whom pregnancy was preserved, compared with patients who had an abortion ($p < 0.05$). Termination of pregnancy in patients with stage III melanoma in both the 1st and 2nd half of pregnancy does not change the progressive course of melanoma.

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