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The occurrence of different types of depression in patients with cervical cancer

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The information that a person is suffering from a severe and life-threatening disease, sudden hospitalization, surgical intervention and other treatment options threatening the bio-psycho-social integrity of an individual may pose a stressful situation that may result in acute stress reaction or adjustment disorders.

The global aim of the research was to examine the impact of the type of cervical cancer therapy on the psychological status of patients and the occurrence of depression.

The basic principle of the research is a comparative analysis of the results obtained using instruments to assess the degree of depression in the experimental and control groups. Within the first experimental group, a comparison was made between patients who underwent surgery and postoperative chemoradiation. Within the second experimental group, a comparison was made between patients who were not operated on but underwent radical chemoradiation. The following

research instruments were used: semi-structured psychiatric interview, gynecological parameters - local findings and stage of the disease, Hamilton scale for depression.

Univariate logistic regression analysis showed that patients before surgery (OR=24.17; 95%PI: 4.81-121.57 and $p<0.001$) and patients before radical chemoradiation (OR=45.99; 95%PI: 8.70-243.15 and $p<0.001$) had significantly higher risk of depression than women from the control group.

Radical hysterectomy is accompanied by an increase in depression in the preoperative period as well as after the operative treatment. Radical chemoradiation leads to an increase in depression to a greater degree compared to radical hysterectomy in the period before and after the treatment.

- Key words: cervical cancer, depression, therapy

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Pojava različitih vrsta depresije kod pacijenata sa karcinomom grlića materice

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Informacija da osoba boluje od teške i po život opasne bolesti, iznenadne hospitalizacije, hirurške intervencije i drugih mogućnosti lečenja koje ugrožavaju bio-psiho-socijalni integritet pojedinca mogu predstavljati stresnu situaciju koja može dovesti do akutne reakcije na stres ili poremećaja prilagođavanja.

Globalni cilj istraživanja bio je da se ispita uticaj vrste terapije karcinoma grlića materice na psihološki status pacijenata i pojavu depresije.

Osnovni princip istraživanja je komparativna analiza rezultata dobijenih korišćenjem instrumenata za procenu stepena depresije u eksperimentalnoj i kontrolnoj grupi. U okviru prve eksperimentalne grupe izvršeno je poređenje pacijenata koji su podvrgnuti operaciji i postoperativnoj hemoradijaciji. U okviru druge eksperimentalne grupe urađeno je poređenje pacijenata koji nisu operisani, ali su podvrgnuti radikalnoj hemoradijaciji. Korišćeni su sledeći instrumenti istraživanja: polustrukturirani psihijatrijski intervju, ginekološki parametri – lokalni nalazi i stadijum bolesti, Hamiltonova skala za depresiju.

Univarijantna logistička regresiona analiza je pokazala da su pacijenti pre operacije (OR=24,17; 95%PI: 4,81-121,57 i p<0,001) i pacijenti pre radikalne hemoradijacije (OR=45,99; 95%PI: 8,70-243,15 i p<0,001) imali značajno veći rizik od depresije u kontrolnoj grupi.

Radikalna histerektomija je praćena porastom depresivnosti u preoperativnom periodu kao i nakon operativnog lečenja. Radikalna hemoradiacija dovodi do povećanja depresivnosti u većem stepenu u odnosu na radikalnu histerektomiju u periodu pre i posle tretmana.

Ključne reči: karcinom grlića materice, depresivnost, terapija

The occurrence of different types of depression in patients with cervical cancer

Introduction

Globally, cervical cancer is the fourth most common cancer in women, with around 660 000 new cases in 2022. In the same year, in low- and middle-income countries, about 94% of the 350 000 deaths caused by cervical cancer (1). Cervical cancer has good prognosis if diagnosed and treated at an early stage of disease. It is necessary for a multidisciplinary team to examine the patient and determine the type of therapy for the patient, which can be surgery, radiotherapy, and systemic therapy. Also, psychological support is very important. (2,3). Genitals, along with secondary sex characteristics, denote biological gender of an individual and gender identity is formed during the developmental process. Patients hospitalized for somatic illnesses may develop autonomic and emotional dysregulation as a consequence of numerous factors, including illness uncertainty, its course, therapy and outcome, dependency of care, as well as accompanying physiological impairments of the somatic disease and its treatment. Just the information that a person is suffering from a severe and life-threatening disease, sudden hospitalization, surgical intervention and other treatment options threatening the bio-psycho-social integrity of an individual may pose a stressful situation that may result in acute stress reaction or adjustment disorders (4-9).

In addition to the described changes, hysterectomy triggers numerous penetrating fears related to injury and destruction, being placed in a dependent position, helplessness, fear of cancer, death, separation fear related to leaving a significant person, fear of losing sphincter control, also specific fears related to the impact of the operation on sexual functioning. Risk factors for the occurrence of depressive disorders in patients with cancer are: earlier mood disorders, alcoholism, advanced stage of cancer, the presence of inadequately controlled intense pain, the existence of a gross somatic disease or complication, the use of chemotherapy known to cause depression. Hysterectomy leads to real losses (loss of organs, menstruation, and ability to give birth) but also symbolic losses in the field of social, family, sexual and professional functioning. All kinds of loss, and this one as well, should be acknowledged, pain should be shared with the right people around you, one should allow the grief run its course and prevent depression onset after surgery. A significant mood shift, such as depression, usually occurs on postoperative days 4 or 5, which can be understood as a part of grieving process referred to as anticipatory grief (9-15)

Aim

The global aim of the research was to examine the impact of the type of cervical cancer therapy on the psychological status of patients and the occurrence of depression. Special attention was paid to the impact of surgical treatment on patients who underwent surgery compared to patients who did not undergo surgery for medical and personal reasons. According to data from the literature on possible types of psychological reactions in patients with cervical cancer, the degree of depression related to the type of therapeutic procedure was analyzed.

Special attention is paid to the possible influence of control variables, age, education, socio-economic status, marital status, personality (extroversion, neuroticism, introversion) of constitutive factors related to the respondents: first menstruation, cycle-regular, irregular, prolonged, shortened, number of births, number of abortions, menopause, year of first intercourse, number of partners until diagnosis, infections and whether they were treated, habits - smoking, alcohol, using contraceptives, going to the gynecologist, colposcopic examination, Papanicolaou test.

Methods

The basic principle of the research is a comparative analysis of the results obtained using instruments to assess the degree of depression in the experimental and control groups. Within the first experimental group, a comparison was made between patients who underwent surgery and postoperative chemoradiation. Within the second experimental group, a comparison was made between patients who were not operated on but underwent radical chemoradiation.

Experimental group I consisted of 30 patients who underwent surgery and in whom cytostatic monochemotherapy cisplatin in a dose of 40mg/m2 was applied along with postoperative radiation therapy. Experimental group II consisted of 30 patients who were not operated on and in whom cytostatic monochemotherapy cisplatin, also at a dose of 40mg/m2, was applied along with radical combined radiation therapy. The control group consisted of 30 healthy subjects.

Criteria for entering the research were: age of 30-60 years, completed minimum secondary education, marital status - married, presence of malignant lesions on the cervix, absence of serious somatic diseases, absence of serious psychiatric disorders treated in hospital in personal history. The research was conducted in the Gynecology and Obstetrics Clinic and the Oncology Clinic of the University Clinical Center of Niš.

The following research instruments were used: semi-structured psychiatric interview, gynecological parameters - local findings and stage of the disease, Hamilton scale for depression The semi-structured psychiatric consisted of: 1. A list of general socio-demographic and medical history data that includes: first and last name, age, marital status, education. 2. Psychosocial functioning. Gynecological parameters included: age at the time of first menarche, cycle duration, period between cycles, age at first birth, number of births, number of abortions, year of first sexual intercourse, number of sexual partners, infections during life, visits to the gynecologist, type of gynecological procedures performed reviews.

The Hamilton scale for depression was constructed due to the need to standardize the phenomenology of the depressive syndrome and to assess the severity of the depressive disorder. The scale is used in clinical and pharmacological studies. It is suitable for quantifying the intensity

of depressive symptoms, and it is also a standard for evaluating the validity of other scales in measuring depression. The basic characteristics of the scale are that it is not too long, it covers the most important symptoms for assessing depression, and it is reliable even when used by two examiners. The Hamilton depression assessment scale belongs to the group of individual scales and is completed by the examiner himself. It is used in two original versions, one with 21 items and the other with 17, with the following score: - 0-7 without depression - 8-15 minor depression - 16 and over major depression. The total score of the Hamilton scale (21 items) determines the severity of depression as follows: - less than 8, depression is not present - from 17 to 24, moderate depression, patients treated in outpatient conditions - more than 24 represents severe depression and is about hospitalized patients. The absence of depression can be assessed if the total score at the end of the treatment or examination is 50% lower than the initial one. The scale is reliable, especially when it comes to average scores. In order to properly fill out this instrument, it is necessary to strictly adhere to the instructions that define the way of conducting the interview, the questions from the scale and the scoring of individual answers.

The Excel program from the Microsoft Office program package was used for entering, ranking, grouping, tabular and graphical presentation of data. Calculations were made using the SPSS program and the Statcalc program from EPI-INFO program package.

Results

Table 1. Average values of the Hamilton scale for depression (Xsr±SD), by groups and time of testing

Group	Testing time			Comparison by test time (Danetov test)
	Before therapy	After 3 months	After 3 months	
Patients who underwent surgery	6.73±3.73	9.47±4.34	12.33±4.31	I vs II: p=0.034 I vs III: p<0.001 II vs III: p=0.038
Patients underwent radical chemoradiation	9.50±4.10	12.53±4.40	16.23±3.48	I vs II: p=0.023 I vs III: p<0.001 II vs III: p=0.002
Control group	3.00±2.39	…	…	-
Group comparison	Dunnett's test I vs II: p=0.025 I vs III: p<0.001 II vs III: p<0.001	Mann-Withney U test Z=3.66 i p<0.001	Mann-Withney U test Z=4.29 i p<0.001	

In the first group, the average value of the Hamilton scale for depression before therapy was 6.73±3.73, then it significantly increased 3 months after surgery to 9.47±4.34 (ANOVA and Dunnett's test: p=0.034), and 6 months after surgery increased significantly once and reached a value of 12.33±4.31 (ANOVA and Danet's test: p=0.038). In the second group of patients, the average value of the Hamilton depression scale also increased significantly, from 9.50±4.10 before the start of therapy to 12.53±4.40 three months later (ANOVA and Dunnett's test: p=0.023) and 16.23±3.48 six months later (ANOVA and Dunnett's test: p=0.002). In the control group, the average value of Hamilton depression scale was 3.00±2.39. At the first test, the value of the depression scale in patients who were assigned to radical chemoradiation was statistically significantly higher than in patients who were assigned to surgery (ANOVA and Dunnet's test: p=0.025) and in the control group (ANOVA and Dunnet's test: p< 0.001).

Patients who were determined for surgery had a significantly higher average value of the depression scale than subjects from the control group (ANOVA and Dunnett's test: p<0.001). When re-testing after three and six months, the value in patients who treated with radical chemoradiation remains significantly higher compared to women who were operated. (Mann-Whitney U test: Z=3.66, i.e. Z=4.29 and p<0.001) (table 1).

Table 2. Comparison of the resulting differences in the values of the Hamilton scale for depression within groups (Xsr±SD), by the time of testing

Grupa	Differences between average scale values		
	Before therapy vs after 3 months	After 3 months vs after 6 months	Before therapy vs after 6 months
Patients who underwent surgery	2.73±2.86	2.87±2.78	5.60±3.52
Patients underwent radical chemoradiation	3.03±2.57	3.70±3.24	6.73±3.62
Man-Vitni U test	ns	ns	ns

The average values of the Hamilton scale for depression in patients who underwent radical chemoradiation increased to a greater degree than in patients who were treated surgery, but the differences between the compared groups in this sample were not statistically significant (table 2).

Table 3. Representation of certain degrees of depression by group and time of testing

Group	Degree of depression	After 3 months			Comparison by test time (Friedman's test)
		Before therapy	Afrer 3 months	After 6 months	
Patients who underwent surgery	Without depression	11 (36.70%)	7 (23.30%)	5 (16.70%)	χ^2=15.93 p<0.001
	Moderate	18 (60.00%)	19 (63.30%)	19 (63.30%)	
	Severe	1 (3.30%)	4 (13.30%)	6 (20.00%)	
Patients underwent radical chemoradiation	Without depression	7 (23.30%)	5 (16.70%)	1 (3.30%)	χ^2=22.69 p<0.001
	Moderate	20 (66.70%)	19 (63.30%)	16 (53.30%)	
	Severe	3 (10.00%)	6 (20.00%)	13 (43.30%)	
Control group	Without depression	28 (93.30%)	…	…	-
	Moderate	2 (6.70%)	…	…	-
	Severe	-	…	…	-
Comparison by groups (Mantel-Hencel ili Fišerov test)	Without depression	I vs II: ns I vs III: χ^2=20.8 i p<0.001 II vs III: χ^2=29.7 i p<0.001	ns	ns	

	Moderate	I vs II: ns I vs III: χ^2=18.9 i p<0.001 II vs III: χ^2=22.9 i p<0.001	ns	ns	
	Severe	I vs II: ns I vs III: ns II vs III: ns	ns	χ^2=3.71 p=0.054	

Moderate depression according to the Hamilton scale was present before the start of therapy in 60.00% of patients who were treated surgery, and severe depression in 3.33% of cases. Three months after the operation, the prevalence of moderate depression in this group rises to 63.33%, and severe depression to 13.30%. After six months, the frequency of moderate depression remains at the same level, and the frequency of severe depression rises to 20.00%. The Friedman test shows a significant difference in the representation of different degrees of depression between repeated tests (χ2=15.93 and p<0.001).

In the group of patients who were treated with radical chemoradiation, moderate depression before the start of therapy was present in a slightly higher percentage (66.70%), as well as pronounced (10.00%). After three months, the prevalence of moderate depression decreased to 63.30%, while the prevalence of severe depression increased to 20.00%. After six months, the share of women with moderate depression decreased to 53.30%, while the share of those with severe depression increased to 43.30%. In this group as well, Friedman's test shows a significant difference in the representation of different degrees of depression between repeated tests (χ2=22.69 and p<0.001).

There were no significant differences between the prevalence of certain degrees of depression in the group of patients who underwent surgery and patients underwent radical chemoradiation before the start of therapy and after three months. After 6 months, the proportion of women with severe depression in the second group was more than twice as high as in the first group (43.30%:20.00%). The Mantel-Hencel Chi square test confirms that this difference in the prevalence of severe depression is at the limit of statistical significance among the examined groups (χ2=3.71 and p=0.054).

In the control group, moderate depression was present in 6.70% of the subjects, and severe depression was not registered. The percentage of women without depression in this group is significantly higher than in the first group (χ2=20.8 and p<0.001) and second group (χ2=29.7 and p<0.001), while the percentage of women with moderate depression in the control group is significantly lower than patients who underwent surgery (χ2 =18.9 and p<0.001) and radical chemoradiation (χ2=22.9 and p<0.001) (table 3).

Table 4. Correlation between the values of the Hamilton scale for depression and individual control and constellation factors at the first test, results of univariate logistic regression analysis

Factor		OR	95%IP		*P*
			lower	upper	
Group	Control	1.00	Reference		
	Before surgery	24.17	4.81	121.57	p<0.001
	Before HRT	45.99	8.70	243.15	p<0.001
Age		1.00	0.92	1.08	0.96
School education	Secondary	3.32	0.83	13.21	0.09
	High school	1.00	Reference		
Menarche (year)		1.34	0.98	1.83	0.07
Cycle duration (day)		0.87	0.61	1.23	0.43
Period between cycles (day)		0.98	0.83	1.16	0.84
Age at first birth (year)		0.96	0.86	1.09	0.61
Number of births		1.63	0.89	2.98	0.11
Number of miscarriages		1.05	0.86	1.28	0.58
First sexual intercourse (year)		0.97	0.77	1.24	0.86
Number of sexual partners		0.60	0.34	1.08	0.09
Smoking status	Smoker	0.81	0.35	1.89	0.64
	Non smoker	1.00	Reference		
Infections	Yes	0.36	0.15	0.86	0.02
	No	1.00	Reference		
Contraceptions	Preservative	0.15	0.01	1.33	0.09
	Pills	1.71	0.66	4.43	0.26
	No contraceptions	1.00	Reference		
Visits to the gynecologist	Twice a year	1.00	Reference		
	Once a year	2.00	0.17	22.94	0.58
	Once in 2 years	3.63	0.35	37.44	0.28
	More than 5 years	7.74	0.84	71.29	0.07
Medical examinations	Never	1.00	Reference		
	Once	0.96	0.33	2.81	0.95
	Once a year	0.11	0.01	1.14	0.07
	Twice a year	0.13	0.02	0.71	0.02
	Periodically	1.14	0.28	4.54	0.85

Univariate logistic regression analysis showed that patients before surgery (OR=24.17; 95%PI: 4.81-121.57 and p<0.001) and patients before radical chemoradiation (OR=45.99; 95%PI: 8.70-243.15 and p<0.001) had significantly higher risk of depression than women from the control group (table 4).

Subjects who went for examinations once every two years had a significantly lower risk of developing depression than women who never had an examination (OR=0.13; 95% CI: 0.02-0.71 and p=0.02).

The multivariate regression model included all the factors that the univariate logistic regression analysis showed to influence the onset of depression with an estimation error probability of less than 0.1 (10%), i.e.: group, schooling, age of first menstruation, number of sexual partners, infections, use of contraception, visits to the gynecologist and examinations (table 4).

Table 5. Correlation between the values of the Hamilton scale for depression and individual control and constellation factors at the first test, results of multivariate logistic regression analysis

Factor		OR	95%IP		*P*
			Lower	Upper	
Group	Control	1.00	Reference		
	Before surgery	31.07	5.64	170.96	p<0.001
	Before HRT	52.19	9.17	296.84	p<0.001
Infections	Yes	0.26	0.08	0.84	0.02
	No	1.00	Reference		

By step-by-step backward (Backward Wald) from the multivariate model, all those factors that did not show a significant influence on the occurrence of depression were excluded, so in the last step, the following were defined as statistically significant: group and previous infections. In patients before surgery, the risk of developing depression was 31 times higher than in the control group (OR=31.07; 95% CI: 5.64-170.96 and p<0.001), while in patients before radical chemoradiation the risk was even 52 times higher than in women. from the control group (OR=52.19; 95% CI: 9.17-296.84 and p<0.001) (table 5). In subjects who had infections, the risk of depression was 4 times lower than in those without infections (OR=0.26; 95% CI: 0.08-0.84 and p=0.02) (table 5).

Table 6. Correlation between Hamilton depression scale values and clinical factors at the first test, results of univariate logistic regression analysis

Factor		OR	95%IP		*P*
			Lower	Upper	
First symptom	Bleeding during sexual intercourse	3.42	1.33	8.76	0.01
	Acyclic bleeding	2.71	0.65	11.23	0.17
	Increased secretion	0.48	0.20	1.11	0.09
	Painful	9.75	3.54	26.82	p<0.001
	Irregular menstrual bleeding	4.32	1.72	10.82	0.002
Time to see a doctor longer than 6 months		0.76	0.22	2.59	0.67
talk openly about the disease		1.36	0.42	4.32	0.60
Stage of disease	Ib	1.00	Reference		
	IIb	1.73	0.44	6.72	0.42
	IIIb	3.18	0.59	17.08	0.18

Bleeding during intercourse significantly increases the risk of depression (OR=3.42; 95% CI: 1.33-8.76), as well as pain (OR=9.75; 95% CI: 3.54-26.82) and irregular menstrual bleeding (OR=3.42; 95 %IP: 1.33-8.76). The time to see a doctor, the attitude of the subjects towards the

disease and the stage of the disease have not been proven as factors that significantly influence the occurrence of depression before the start of therapy.

During the second and third testing, none of the control, constellation and clinical factors, as well as belonging to one of the investigated groups, had a significant impact on the change in the category of the level of depression (no depression / moderate or severe depression). At the second test, only pain caused an increased risk for the occurrence of moderate or severe depression, but at the level of the probability of an error of the statement less than 0.1 or 10% (OR=3.65; 95%IP: 0.96-13.90 and p=0.058) (table 6).

Discussion

Cancer is related to depression which is a pathological affective response to loss of normality as a result of cancer diagnosis, treatment or forthcoming complications. Depression presents itself with symptoms of sadness, feelings of fear and panic and longing for the lost object (organ), it is accompanied by dysfunction increase, feeling of worthlessness and low self-esteem, suicidal preoccupations or inability to accept anything with pleasure (16-19). In our research, a higher percentage of patients treated with radical chemoradiation openly talk about their illness, but the difference compared patients who underwent surgery in the examined sample is not statistically significant. In patients who were surgically treated, the average value of the Hamilton depression scale before therapy was 6.73±3.73, then it increased significantly three and six months after surgery. The average value of the Hamilton depression scale also increased significantly in patients who underwent radical chemoradiation, from 9.50±4.10 before the start of the therapy, after three and six months after the completion of the therapy. At the first test, the value of the depression scale in patients who were assigned to radical chemoradiation was statistically significantly higher than in patients who were assigned to surgery, as well as in the control group, which agrees with data from the literature (20). When re-tested, the value in patients who underwent radical chemoradiation remained significantly higher than in patients who underwent surgical treatment.

In study Aziza at al. the HADS measurement showed that patients with cervical cancer have mild and severe levels of anxiety and depression. The results of this study also confirmed that emotional functioning, fatigue and insomnia were the main predictors of anxiety and depressive disorders in women with cervical cancer (4). Zhao et al. showed in their study that the prevalence of anxiety and depression was 44.9% and 36.1% in cervical cancer patients who underwent surgery. Compared to healthy individuals, patients with cervical cancer had a higher prevalence and worse severity of anxiety and depression They also stated that the presence of cervical cancer and the fear of recurrence of cervical cancer may cause severe psychological burden and worsening anxiety/depression in patients with cervical cancer who have undergone surgery. Impairment of physical and social functions, financial burden of treatment, and psychological stress of surgery may also lead to the prevalence and severity of anxiety/depression in cervical cancer patients undergoing surgery. Their study found that diabetes, FIGO stage II were independent predictors for a higher risk of anxiety, and diabetes and lymph node metastases were independent predictors for an increased risk of depression in cervical cancer patients undergoing surgery. It has been shown that a higher stage of the disease can cause a higher level of anxiety and depression (21). In accordance with the study by Zhao and our study, Tosic Golubovic et al.

showed that depression and anxiety scores were relatively high among a group of patients with cervical cancer. The levels of anxiety and depression severity were different between the studied groups and FIGO stages. In the group with more advanced FIGO stage of the disease, depression scores were higher (22). Environmental factors play a role in determining whether a vulnerable woman may develop depression major or generalized anxiety disorder, meaning that there is an environmental factor (not related to genetic factors) that is only depressogenic or only anxiogenic. Anxiety and depression are associated common comorbidities in cancer patients and may affect patients' survival. Providing appropriate information and social support may have a role in patients' psychological well-being, but different patients may favour different information and life style. In assessing clinical features of depression in patients with somatic diseases it is very important to take the full medical history that indicates the presence of depression symptoms, excludes the presence of some other psychiatric disorder, as well as the presence of psychosocial factors associated with depression (23-28).

The result of the Dhakal et al. (29) review showed that various methods (such as exercise, telephone counseling, educational brochure, family education, consultation sessions, lecture presentations, self-study package, face-to-face interviews, medication, psychotherapy, nurse support) can contribute to the effectiveness in solving the psychological support care needs "anxiety and depression" of cervical cancer patients. Very often, due to the lack of understanding of the situation and condition female patients face, there are wrong interpretations that trigger unnecessary fear, suspicion and premonition. Patients with anxious personality trait greatly correlate with preoperative anxiety onset, but also with ongoing anxiety after hospital discharge, along with increased depression, fatigue, low frustration tolerance threshold, resulting in frequent visits to the doctor. Assessment measures conducted in studies (30-33) determined the range of emotional disturbances. The results of these studies show that simply talking with patients may be useful in revealing women at risk of anxiety, depression, or both.

Conclusion

Radical hysterectomy is accompanied by an increase in depression in the preoperative period as well as after the operative treatment. Somatic disorder and hospitalization are crisis events that trigger the feeling of helplessness, risk of loss and passive position, as well as adjustment disorder with dominant depressed mood as clinical manifestation. Radical chemoradiation leads to an increase in depression to a greater degree compared to radical hysterectomy in the period before and after the treatment.

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