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Management of idiopathic recurrent pericarditis during pregnancy

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ABSTRACT

Background: Data concerning idiopathic recurrent pericarditis in pregnancy are scarce.
Objectives: To evaluate the management and outcome of idiopathic recurrent pericarditis during pregnancy.
Methods and results: Twenty-one pregnancies were evaluated in fourteen women with a history of recurrent idiopathic pericarditis (mean maternal age 31.5 years, mean gestational age 39.0 weeks), and subdivided in 2 cohorts: eight pregnancies were analyzed retrospectively (2002−2010), thirteen (2011–2017) prospectively and followed according a predefined management protocol. Ten pregnancies were uneventful, three ended in spontaneous early abortion, one fetal death occurred at 19 weeks. Recurrences of pericarditis occurred in eight and were treated by adding NSAIDs in two cases; in five cases the dose of corticosteroids was increased and in two cases aspirin was started/increased; paracetamol was always allowed. Colchicine was used in two cases in the prospective cohort. HELLP syndrome occurred in one patient, which resolved after delivery, and one patient experienced arterial hypertension and elevated transaminase. All infants had a good outcome (mean birth weight 3114 g, 10 males). Birth weight was significantly lower in the retrospective cohort (respectively 2806 g vs. 3320 g, *p*-value 0.017) in which higher doses of corticosteroids were used (median dose respectively 10.0 mg vs. 2.5 mg, *p*-value 0.048). Five recurrences of pericarditis occurred after delivery, easily treated with standard therapy.
Conclusion: General outcomes of pregnancy in patients with idiopathic recurrent pericarditis is good, especially when patients are carefully followed by multidisciplinary teams according to standardized protocols.

1. Introduction

Pericardial involvement is sporadic during pregnancy, and pregnant women do not show any predisposition to pericardial diseases [1]. As in the general population, acute pericarditis and recurrent pericarditis are the most common pericardial diseases requiring medical therapy in pregnant women and the etiology remains in most cases not defined [1,2]. The evidences on recurrent pericarditis during pregnancy are very limited, and management strategies are mainly based on a few case reports and expert's opinion. However, particularly in pregnant patients, the choice of medical therapy is an important issue. Unfortunately, pericarditis is not mentioned by the recently published European guidelines on the management of cardiovascular diseases during pregnancy [3]. Nowadays the largest study on this topic is a retrospective report of six pregnancies that was published in 2010 [4]. Aim of the present paper is to evaluate the management and outcome of idiopathic recurrent pericarditis (IRP) during pregnancy and lactation in a larger case series of twenty-one pregnancies, describing also the management protocol we have adopted from 2011, starting from our experience in the management of pregnancy in rheumatic autoimmune diseases.

2. Methods

2.1. Setting

The entire sample was subdivided in two cohorts, the first cohort from 2002 till 2010 of eight pregnancies were analyzed retrospectively, the second cohort from 2011 till 2017 of thirteen pregnancies were analyzed according a prespecified prospective protocol.

2.2. Patient population

All pregnant patients with a history of IRP were included. The diagnosis was based on the usual criteria for recurrent pericarditis proposed by the current guidelines: a documented first attack of acute pericarditis, a symptom-free interval of six weeks or longer,

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and evidence of subsequent recurrence of pericarditis [5–10]. The condition was considered idiopathic based on a previous extensive diagnostic work-up performed according to guidelines [10,11] before the index pregnancy. In all the women C reactive protein was elevated during the attacks. Women with a single unique episode of acute pericarditis occurring during pregnancy were not included.

The study is conducted in accordance with the declaration of Helsinki and approved by the ethical committee of Ospedale Papa Giovanni XXIII, Bergamo. All participating patients gave informed consent. Six of the included pregnancies have already been described in a previous report [4].

2.3. Data collection and follow up

Starting from 2011 we adopted a formal prospective protocol, including the recording of baseline demographics, pregnancy course and maternal outcome, fetal outcome including birth weight, length and APGAR score five and 10 min after delivery, maternal outcome and recurrences of pericarditis. The following adverse events were recorded: recurrences of pericarditis during pregnancy or during the first year after delivery, miscarriages, preeclampsia and related conditions, such as HELLP (haemolysis, elevated liver enzyme levels, and low platelet levels) syndrome and other relevant complications during pregnancy. Starting form 2011 we also formally suggested a standard therapeutical protocol, described in Table 1. Medical assessment was scheduled approximately every month, together with Gynaecologists expert in the management of pregnancy at risk.

2.4. Statistical analysis

Descriptive statistics were used to describe the basic features and performed utilizing IBM© SPSS Statistics, version 25. The descriptive statistics are presented as mean or median, interquartile range (IQR) values and measured ranges indicate minimums and maximums. A chi-square test was used to compare categorical variables between the two cohorts and between the use of corticosteroids, while continuous variables were analyzed with the two-tailed Student's *t*-test. The Fisher's Exact was used instead of the chi-square test in case the expected cell count was less than five.

3. Results

Twenty-one pregnancies were evaluated in fourteen women with a history of IRP from 2002 till 2017. Mean number of recurrences before the index pregnancy was 9.9 (range, 1–30) (the first pregnancy in case of multiple pregnancy in the same women), with a clinical history of recurrent pericarditis lasting 64.3 months on average (range, 2–288 months).

Mean maternal age was 31.5 years (±4.1, range 25.0–38.0 years), mean gestational age 39.0 weeks (±2.0, 37.0–41.0 weeks). Baseline characteristics and comparison between the cohorts are reported in Table 2. Table 3 comprises main data in each pregnancy.

3.1. Treatment during pregnancy

Prednisone was used at low to moderate doses in thirteen pregnancies: more frequently and at higher dosage in the retrospective cohort (median dose respectively 10.0 mg in the retrospective cohort vs. 2.5 mg in the prospective cohort, *p*-value 0.048).

Aspirin was used in addition to corticosteroids in eleven pregnancies: in four cases at a dose of 500–800 mg every 8 h. In three of these pregnancies aspirin was stopped at gestational week twenty, while in the fourth case aspirin was continued at high-dose till delivery (patient 3 in Table 3, retrospective cohort); this woman developed an HELLP syndrome. Aspirin was used at a lower dose, 100 mg, in the other seven pregnancies, and continued till delivery.

Indomethacin and ibuprofen were used in one pregnancy each in the prospective cohort and stopped before gestational week twenty. Colchicine was used in two cases in the prospective cohort.

No therapy was given during three pregnancies, and only paracetamol was given in one pregnancy.

3.2. Pregnancy outcomes

Seventeen deliveries occurred (10 male infants) and four miscarriages. These latter were due to one fetal death at 19 weeks and in three cases early spontaneous abortions occurred within the first twelve weeks. One patient with a miscarriage used corticosteroids and aspirin, the other three patients used no medication prior to the miscarriage.

During gestation one patient in the prospective cohort experienced mild hypertension and mild elevation of transaminase (twice the normal values), this was effectively treated with methyldopa 250 mg twice daily. Further, we observed one HELLP syndrome in the retrospective cohort that developed in the mother in which high dose aspirin was continued till delivery, with rapid improvement after delivery. All infants had a good outcome with a mean birth weight of 3114 g (±432, 2284–4040 g), with one infant small for gestational age (2284 g at gestational age 40 weeks).

3.3. Clinical course of pericarditis (Tables 2 and 3)

Pericarditis recurred during pregnancy in eight women. None of the recurrences we observed required hospital admission, but of course hospitalization should be considered on an individualized basis in the presence of high-risk criteria according to the current guidelines and according to the maternal and fetal clinical conditions.

The recurrences were treated by adding non-steroidal anti-inflammatory drugs (NSAIDs) in two cases and in five cases corticosteroids were increased and aspirin started/increased. Additional treatment with paracetamol were also allowed. Other five recurrences of pericarditis occurred after delivery, easily treated with standard therapy (ibuprofen, indomethacin, colchicine, paracetamol). Only mild pericardial effusions were recorded, clinically not significant.

3.4. Comparison between retrospective and prospective cohorts

Comparing the retrospective cohort (eight pregnancies from 2002 till 2010) with the prospective cohort (thirteen pregnancies from 2011 till 2017) birth weight was significantly lower in the retrospective

Table 1
A proposed treatment scheme for medical therapy of pericarditis during pregnancy.

Drug	Pregnancy		After delivery
	<20 weeks	>20 week	During breastfeeding
Aspirin[a] 250 to 750 mg every 8 h	Allowed	To be avoided	Preferably avoided
NSAIDs (ibuprofen, indomethacin, naproxen)	Allowed	To be avoided	Allowed
Paracetamol	Allowed	Allowed	Allowed
Prednisone 2,5 to 10 mg daily, at the lowest effective dose	Allowed[b]	Allowed[b]	Allowed[b]
Colchicine	Allowed	Allowed	Allowed

Pregnancy should be planned in a phase of disease quiescence and followed by multidisciplinary teams with experience in the field. During pregnancy tapering of therapy should be extremely cautious. Normal vaginal delivery is possible and should be considered in absence of contraindications.
During pregnancy and breast feeding anti-histamine H2 blockers or proton pump inhibitors (PPI) may be used.
Supplementation with calcium and vitamin D (1500 mg/day and 800 IU/day, respectively) should be offered to all women taking corticosteroids in pregnancy and lactation.
[a] Low-dose aspirin is not expected to have substantial anti-inflammatory activity but may reduce the risk of preeclampsia in women at risk [22].
[b] Possible association with aspirin or a NSAID; prednisone and prednisolone are metabolized by the placenta into inactive 11-keto forms, and only 10% of the active drugs may reach the fetus.

Table 2
Overview of baseline characteristics, medication and pregnancy outcome of total cohort and a comparison between the two sub-cohorts.

Total $n = 21$	Total cohort $n = 21$		Retrospective cohort 2002–2010 $n = 8$		Prospective cohort 2011–2017 $n = 13$		p-Value
Demographics							
Maternal age, mean (SD, range)	31.5	(±4.1, 25.0–38.0)	29.0	(±2.9, 25.0–33.0)	33.0	(±4.0, 25.0–38.0)	0.024
Gestational age* (weeks), mean (SD, range)	39.4	(±2.1, 37.0–45.0)	38.5	(±1.2, 37.0–40.0)	39.9	(±2.3, 38.0–45.0)	0.194
Treatment during pregnancy							
Prednisone	13	(61.9%)	7	(87.5%)	6	(46.2%)	0.085
Median dosage prednisone (IQR, range)	7.5	(IQR 17.5, 2.0–25.0)	10.0	(IQR 20.0, 5.0–25.0)	2.5	(IQR 7.38, 2.0–15.0)	0.048
Aspirin	11	(52.4%)	4	(50.0%)	7	(53.8%)	1.000
Of which low dose (100 mg/day)	5	(23.8%)	0	(0%)	5	(38.5%)	0.111
NSAIDs	3	(14.3%)	0	(0%)	3	(23.1%)	0.257
Colchicine	2	(9.5%)	0	(0%)	2	(15.4%)	0.243
Acetaminophen	5	(23.8%)	0	(0%)	5	(38.5%)	0.111
Pregnancy outcomes							
Live births	17	(81%)	6	(75.0%)	11	(84.6%)	0.586
Pre-term (<37 weeks)	1	(4.8%)	1	(12.5%)	0	(0%)	0.191
Early term	5	(23.8%)	3	(37.5%)	2	(15.4%)	0.248
Full term	9	(42.9%)	2	(25.0%)	7	(53.8%)	0.195
Postterm	2	(9.5%)	2	(25.0%)	0	(0%)	0.243
Early abortions (<12 weeks)	3	(14.3%)	2	(25.0%)	1	(7.7%)	0.271
Fetal deaths (>12 weeks)	1	(4.8%)	0	(0%)	1	(7.7%)	0.421
Cesarean section	6	(28.6%)	2	(25.0%)	4	(30.8%)	1.000
Gestational hypertension	1	(4.8%)	0	(0%)	1	(7.7%)	0.421
Preeclampsia/HELLP syndrome	1	(4.8%)	1	(12.5%)	0	(0%)	0.191
Birth weight*, mean (SD, range)	3114.5	(±432.1, 2284–4040)	2806.2	(±322.3, 2284–3250)	3320.0	(±378.2, 2890–4040)	0.017
Clinical course of pericarditis							
Recurrences during pregnancy	8	(38.1%)	1	(12.5%)	7	(53.8%)	0.085
Recurrences within one year after delivery	5	(23.8%)	0	(0%)	5	(38.5%)	0.111

Data are numbers (percentage) unless specified otherwise. * based on live births ($n = 17$ total, retrospective cohort $n = 6$, prospective cohort $n = 11$). Pre-term is defined as delivery within 37 weeks of gestation, early term 37 0/7 weeks through 38 6/7 weeks, full term 39 0/7 weeks through 40 6/7 weeks and postterm >42 weeks.

cohort (respectively 2806 g vs.3323 g, $p = 0.012$) in agreement with the findings that in this cohort corticosteroids were used more frequently and at higher dosages (median dose respectively 10.0 mg vs. 2.5 mg, p-value 0.048) in this cohort (Table 2). On the other hand in the prospective cohort we tried to use lower doses of corticosteroids, using instead indomethacin and ibuprofen. These lower dosages of corticosteroids were associated with more frequent recurrences in our prospective cohort, but these recurrences were mild, and easily treated with aspirin, NSAIDs, paracetamol and in some cases mildly increasing the dosage of corticosteroids, always in a range considered safe for the pregnancy. Colchicine was used by two women during pregnancy and breast feeding only in the prospective cohort.

One woman in the retrospective cohort developed an HELLP syndrome; she was treated with high dose aspirin till delivery; in the prospective cohort use of high dose aspirin/NSAIDs till delivery was not allowed.

4. Discussion

This report describes the largest case series of pregnancies in women with IRP: this topic was not addressed in the recent ESC guidelines on management of cardiovascular diseases during pregnancy [12], and this report aims to fill this gap in evidence. Numbers are still low, but the condition is not frequent and probably in most young women with IRP family planning is not addressed and most of them were counselled in the past to avoid or to postpone pregnancies. A classical approach is to assess two aspects: the effect of the disease on pregnancy (gestational outcomes) and the effect of pregnancy on the disease. Gestational outcomes in our women were good, particularly in the more recent prospective cohort: prematurity 0%, early abortion 7.7%, fetal death 7.7%, cesarean section 30.8% (Table 2), similar to those observed in women with autoimmune or autoinflammatory conditions when prospectively followed by expert multidisciplinary teams [13–16], and similar to those expected in the normal population [17].

Also the clinical course of pericarditis was satisfactory, with some women experiencing mild recurrences during pregnancy or peripartum, always easily treated with modest increase in therapies.

Taking advantage from our experience in the management of pregnancy in women with autoimmune rheumatic disease [1,13,14,18] and re-assessing the findings observed in the retrospective cohort [1], we adopted a protocol (Table 1). Family planning should always be addressed in women with IRP of reproductive age [19]. Pregnancy should be planned in a phase of disease quiescence and followed by multidisciplinary teams with experience in the field [1,4]. Adjustment of therapy should be considered before a planned pregnancy [19]: colchicine use may be discussed with the woman; high dose aspirin or conventional NSAIDs may be added (if needed) till approximately gestational week 20, eventually with low dose prednisone [1,4]. As in general population, folic acid should be added in all cases before conception. Normal vaginal delivery is possible.

In the general population, NSAIDs are recommended as first choice therapy for acute and recurrent pericarditis [7,10]. Several population-based cohort and case-control studies among pregnant patients did not demonstrate an increased risk of congenital malformations in first-trimester use of NSAIDs [18,20]. High dose aspirin is sometimes preferred since it is regularly used in the anti-phospholipid syndrome in pregnancy and is useful in the prevention of preeclampsia in high-risk obstetrical patient [20–22]. However, prostaglandins are important mediators in parturition and NSAIDs can prolong gestation and labor [20]. After gestational week twenty, all NSAIDs (except low dose aspirin ≤100 mg/day) can cause constriction of the ductus arteriosus and can impair fetal renal function and therefore should be withdrawn [1]. If necessary to control pericarditis after gestational week twenty paracetamol, colchicine (see below) and/or very low dose of prednisone (2.5–5 mg) can be substituted. NSAIDs may be restarted during breast feeding, while high-dose aspirin is generally avoided during lactation [18,20].

Glucocorticoids are often used in the setting of pericarditis. The most common used short-acting corticosteroids are prednisone, prednisolone and methylprednisolone; these corticosteroids may be used during

Table 3
Overview main data in the 21 pregnancies.

Nr	Age	Gestational age (weeks)/ birth weight (grams)	Therapy in pregnancy	Recurrences during pregnancy	Recurrences within 1 year after delivery	Treatment for recurrences during pregnancy	Infant outcome	Maternal outcome
Retrospective cohort (2002–2010)								
1	25	38 wk/3250 g	Prednisone 25 mg slowly tapered	No	No	–	Good	Good
2	32	40 wk/3000 g	Prednisone 25 mg slowly tapered	No	No	–	Good	Good
3	31	40 wk/2284 g	Prednisone 10 mg tapered to 5 mg daily + aspirin 800 mg 3× day till delivery	No	No	–	Good	HELLP
4	33	38 wk/2823 g	Prednisone 5 mg tapered to 2.5 mg daily + aspirin 800 mg 3× daily till 21st week	No	No	–	Good	Good
5	26	38 wk/2780 g	Prednisone 10 mg	No	No	–	Good	Good
6	30	37 wk/2700 g	Prednisone 25 mg, with tapering + aspirin 100 mg	Yes, week 20	No	Prednisone	Good	Good
7	28		No therapy	No	No	–	Early abortion <10 weeks	Good
8	27		Prednisone 5 mg 3/week + aspirin 100 mg	No	No	–	Early abortion <10 weeks	Good
Prospective cohort (2011–2017)								
9	32	39 wk/n.a.	Paracetamol	No	Yes, one month after delivery		Good	Good
10	35	39 wk/3130 g	Prednisone 2.5 mg	Yes, week 23	No	Prednisone 7.5 mg, aspirin 100 mg, and paracetamol	Good	Mild hypertension + elevation transaminase
11	37	39 wk/3580 g	Prednisone 2.5 mg + aspirin 100 mg + indomethacin 25 mg (stopped at 19th week), ranitidine	No	Yes, soon after delivery		Good	Good
12	35	39 wk/n.a.	Aspirin 500 mg 2× daily with tapering	Yes, week 11	No	Increased dose of aspirin	Good	Good
13	38	39 wk/4040 g	Prednisone 2.5 mg + aspirin 100 mg + ranitidine	Yes at delivery	No	prednisone 5 mg + indomethacin 25 mg 3× daily	Good	Good
14	25	40 wk/3110 g	Colchicine 1 mg 5 days/week during all the pregnancy and breast feeding	No	No	–	Good	Good
15	32		Prednisone 15 mg, with tapering + paracetamol	Yes, week 14	No	Prednisone increased again to 15 mg tapered in 8 weeks + paracetamol	Fetal death at 19 weeks, due to chorioamnionitis (after corticosteroid therapy)	Good
16	33	38 wk/2890 g	Aspirin 100 mg	No	No		Good	Good
17	29		No therapy	No	No		Early abortion 12 weeks	Good
18	30	41 wk/3720 g	No therapy	Yes, at delivery	No	Paracetamol 1000 mg 3× daily	Good	Good
19	36	38 wk/3000 g	Colchicine 1 mg during all the pregnancy and breast feeding + pantoprazole 40 mg 2× daily	No	Yes		Good	Good
20	29	40 wk/3160 g	Prednisone 5/2.5 mg on alternate day + aspirin 500 mg 3× daily	Yes, week 14	Yes	Prednisone increased to 7,5 mg + paracetamol 1000 mg ×2, aspirin 500 mg ×3, and then gradual tapering	Good	Good
21	38	39 wk/3250 g	Prednisone 2.5 mg 3/week + aspirin 100 mg	Yes, week 20	Yes	Ibuprofen	Good	Good

HELLP = haemolysis, elevated liver enzyme levels, and low platelet levels; mg-milligrams, g = grams, wk = week(s), n.a. not available.

pregnancy since they are metabolized by the placenta into inactive 11-keto forms, and only 10% of the active drugs may reach the fetus [23]. In a meta-analysis Park-Wyllie found a 3.3 fold increased risk of developing oral clefts after first-trimester exposure to corticosteroids. The same study did not show an increased risk of other congenital abnormalities after exposure to corticosteroids [24]. On the whole it is now generally assumed that corticosteroids do not appear to increase the risk of congenital abnormalities in humans [13,18–20], based also on a population-based case-control study [25]. In pregnant women with pericarditis, if corticosteroids are deemed necessary, the lowest effective dose of prednisone (2.5–10 mg/day) should be given combined with supplementation of calcium (1500 mg/day) and vitamin D (800 IU/day). Our results confirm that these low dose corticosteroids are safe. Corticosteroids, particularly at higher dosages, such as in our retrospective cohort, may increase the risk of premature rupture of the membranes and low birth weight [19,20]. On the other hand lower dosages of corticosteroids were associated with more frequent recurrences in our prospective cohort (53.8 vs 12.5%), but these recurrences were mild, and easily treated with modest increase in therapies. In other words the protocol we adopted in the prospective cohort reduced the dosage of corticosteroids, obtaining better fetal outcomes (higher birth weights and less prematurity), that is the first recognized cause of neonatal mortality and long-term neurologic impairments in children [26], at the expense of an increase in the number of

recurrences, that were mild, did not require hospitalizations and were easily treated with mild therapies, including lower doses of corticosteroids. The women we managed are probably a selected sample, with a long clinical history of recurrent pericarditis (64.3 months on average) and many recurrences (9.9 on average), referred to specialized centers; it is possible that in the prospective cohort we now included women that were counselled in the past to avoid pregnancies because of their clinical history or the fear of use colchicine.

In case of acute pericarditis in the general population it is recommended to add colchicine to NSAIDs [10]. Colchicine use in pregnancy has been controversial due to its anti-mitotic properties. The possible effects of colchicine during pregnancy have been previously studied in patients with familial Mediterranean fever (FMF) [15,27] and more recently also in Behcet's disease [28,29]. A meta-analysis of 554 pregnancies with colchicine exposure showed that its use throughout pregnancy was not associated with an increased incidence of miscarriage or major fetal malformations. In women with FMF who took colchicine throughout the pregnancy, there were no significant difference in birth weight or gestational age compared with those who did not take colchicine [30]. In the recent years use of colchicine during pregnancy and breast feeding has become a standard in women with FMF [15,27,28,30], with no signal of danger, and in several countries it is no longer contraindicated during pregnancy [19]. The European League Against Rheumatism (EULAR) task force consider colchicine compatible with pregnancy and breast feeding [19]. For this reason we also adopted the use of colchicine in our protocol (Table 1.) and allowed the use of colchicine till gravindex positivity. After this period continuation during pregnancy and lactation is discussed with the mother if its use is important to control recurrent pericarditis, since an optimal control of the activity of the disease is the main driver of the materno-fetal outcomes. No adverse effects in breastfed infants have been reported in case series and a case-control study and most authors consider colchicine safe during breastfeeding in women being treated for familial Mediterranean fever or rheumatic conditions [19,31–33]. In our prospective cohort, two women took colchicine during pregnancy and breast feeding, both infants had a normal birth weight, without any complications or adverse outcomes.

About 40% of the pregnant women develop a minimal to moderate clinically silent hydropericardium by the third trimester. Usually it is an occasional finding, and the pericardial effusion disappears within 1–2 months following delivery [34]. These women are asymptomatic, and we did not consider to modify the usual criteria for the diagnosis of acute pericarditis [10] in this setting.

5. Limitations

Potential limitations of this study include the observational design, that could lead to treatment bias, and the small number of pregnancies; however this study is the largest case series on this topic.

6. Conclusion

Family planning should be addressed in women with IRP of reproductive age and adjustment of therapy considered before a planned pregnancy. Nowadays the general outcomes of pregnancy in patients with recurrent pericarditis can be similar to the general population, when carefully followed by multidisciplinary teams expert in the field utilizing standardized protocols; our findings may be useful for the counselling and management of women with IRP who wish to have a baby. Larger, controlled studies are warranted to further elucidate the optimal treatment strategies for pregnant patients with recurrent pericarditis.

7. Clinical perspective

The general outcomes of pregnancy in patients with recurrent pericarditis can be similar to the general population, our findings may be useful for the counselling and management of women with IRP who wish to have a baby.

8. Translational outlook

Larger, controlled studies are warranted to further elucidate the optimal treatment strategies for pregnant patients with recurrent pericarditis.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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