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**REVIEW ARTICLE**

# Perinatal complications following excisional treatment of cervical dysplasia

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## Summary

Cervical cancer is one of the most common malignant tumors in women. Mass screenings have significantly decreased its incidence, while causing an increase in precancerous cervical lesions that are mainly diagnosed in women of reproductive age who still have not fulfilled their reproductive goals.

The aim of surgical treatment of these premalignant lesions is to prevent the development of cervical cancer, with minimal risks to the reproductive function. The most important perinatal complication is preterm delivery, usually coupled with preterm premature rupture of the membranes and chorioamnionitis. This results in prematurity with low birth weights, which can further result in increased neonatal morbidity and mortality. Data on the incidence of spontaneous miscarriages in treated women are non-consistent, however, it is believed that the incidence is higher in the second trimester.

Possible predictors of complications are the amount of excised tissue, the type of excision technique, age at the time of surgery, and the length of the period between treatment and conception. Re-excision of the cervix is an additional risk factor for perinatal complications. The risk of perinatal complications is the highest after cold knife conization, followed by laser conization, whereas LEETZ excision means the lowest risk – this is primarily explained by the variations in the cone size.

Having in mind that not all precancerous cervical lesions progress to cancer and that all types of excision treatments are associated with an increased incidence of perinatal complications, an adequate approach would entail primarily well-selected patients, i.e., treating only those women who are at real risk of developing cancer. The surgical treatment must be adapted to provide minimal risks for perinatal complications, maximal oncologic safety, and minimal risk of residual and/or recurring disease during a woman's lifespan.

**Keywords:** cervical dysplasia, excision, perinatal outcome, obstetric complications

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## INTRODUCTION

Cervical cancer is one of the most common cancers in female population worldwide (1). It has been reported that the incidence and mortality rate of cervical cancer have declined in high-resource settings due to vaccination and screening programs as well as the timely treatment of precancerous cervical lesions diagnosed by screening (1). Moreover, mass screenings have resulted in a profound increase in the incidence of cervical premalignant lesions, which are now mainly diagnosed in women of reproductive age (2).

The mean age of women diagnosed with cervical intraepithelial neoplasia (CIN) grade 3 is nowadays 31-34 years in most populations (3). Timely treatment of these premalignant lesions is important for reducing the incidence of cervical cancer with minimal risks of adverse effects on the reproductive function, i.e., infertility, perinatal morbidity, and mortality (3, 4, 5). An increased risk of perinatal complications following cervical conization was demonstrated during the last century (6). Furthermore, surgical treatment of cervical premalignant lesions is associated with additional long-term morbidity in terms of the impairment of psycho-social and emotional well-being, changes in sexual life, which all additionally diminish reproductive outcomes and health-related quality of life (HRQoL) in women affected by cervical dysplasia during reproductive years (7-14).

This narrative review aims to discuss perinatal outcomes in women who underwent a surgical treatment of cervical precancerous lesions.

## METHODS

Authors searched for the available data on obstetrical complications and perinatal outcomes in women treated for cervical precancerous lesions. We searched PubMed, Medline, EMBASE, and Cochrane Library from inception to July 2023. The key words used were ”cervical dysplasia”, ”cervical intraepithelial neoplasia”, ”treatment”, ”pregnancy”, ”morbidity”, ”mortality”, ”pregnancy outcome”, “perinatal complication”, “obstetrical complication”. Only full-length peer-reviewed articles concerning cervical precancerous lesions and perinatal outcomes and complications in women treated for cervical dysplasia were included in the review. Additional articles were identified from the reference section of relevant papers, based on the authors’ estimation. We excluded non-English language studies, case reports and studies, book chapters, editorials, and letters.

## BRIEF HISTORICAL OVERVIEW

The influence of cold knife conization (CKC) of the cervix on women’s reproductive performance has been studied since the 1940s (15). Later studies asserted that CKC was associated with numerous perinatal complications (14, 17, 18, 19).

According to a report published in 1990, data on perinatal complications of large loop excision of the transformation zone (LLETZ) were still unavailable (20). Following initial reports on obstetrical harms caused by LLETZ, several studies indicated that although it was considered to be a small and safe surgical procedure causing a significant decrease in cervical cancer mortality, there was an increased risk of preterm delivery and subsequent complications after LLETZ (6,21). Nevertheless, most of the initial studies on perinatal morbidity associated with LLETZ were observational and conducted on a small number of patients, and the conclusions drawn were equivocal until 2006 when Kyrgiou et al. (18) published a systematic review and meta-analysis. Their publication included a total of 27 retrospective studies, of which ten provided data on the effects of LLETZ, ten on CKC, seven on laser conization, and four on laser ablation. Despite abundant interstudy heterogeneity related to laser conization, the results of the analysis showed that all the excisional procedures were linked to similar pregnancy-related complications. LLETZ was linked to a significantly higher risk of preterm delivery, low birth weight and preterm premature rupture of membranes (PPROM), whereas CKC was associated with a significantly higher risk of preterm delivery, low birth weight, and cesarean section (CS) rate. Importantly, apart from data on the increased rate of perinatal complications associated with cervical excision procedures, this meta-analysis indicated a link between the amount of the excised tissue and unfavorable obstetric outcomes, particularly in relation to cone depth above 10 mm. Moreover, the above-mentioned publication raised the question of perinatal morbidity following treatment with ablative surgical procedures and concluded that these methods also required further evaluation. Later meta-analyses investigated the influence of cervical excisional treatments on pregnancy outcomes (19,22). Two years later, a meta-analysis published by the same research group concluded that CKC and laser conization were connected with an increased risk of perinatal mortality and very low birth weight (<2000gr) in neonates (19). They found a significant association between CKC and perinatal mortality with a relative risk (RR) of 2.87, while LLETZ was also associated with adverse outcomes in relation to perinatal mortality, although without statistical significance - an RR of 1.17. The cited authors estimated that two perinatal deaths occurred in 1000 pregnancies after LLETZ treatment. Bruinsma et al. (22) conducted a meta-analysis aimed to investigate the association between different treatments of cervical precancerous lesions and a risk of preterm birth. These authors reported that excisional treatments of cervical lesions were associated with an increased risk of preterm birth (<37 weeks). Moreover, the authors concluded that the presence of cervical dysplasia was a *per se* risk factor for preterm birth.

In the following years several researchers evaluated pregnancy-related morbidity associated with surgical treatment of cervical premalignant lesions, thus shedding more light on this topic (2,14,23). Later meta-analyses confirmed previously published results in relation to pregnancy outcomes and complications after excisional treatment of cervical premalignant lesions (14). Recent reports have indicated that even multiple cervical biopsies in women of reproductive age might influence preterm delivery rates in women who have undergone such procedures (24).

## PROBABLE CAUSES OF PERINATAL COMPLICATIONS AND THEIR MECHANISMS OF ACTION

Although numerous studies have undoubtedly observed that excisional treatment of cervical precancerous lesions may lead to substantial complications during pregnancy and delivery, it is still not clear what are all the mechanisms that cause these complications (11).

Reduced cervical tissue mass after the treatment is not the only factor causing these complications (25). The removal of the cervical tissue following the use of any of the available excisional treatment techniques leads to structural changes in the uterine cervix. Its weakened mechanical role in supporting pregnancy, sometimes associated with damage in the internal os, together with changes in the cervicovaginal microflora and changed immune milieu of the cervical mucus are the most probable mechanisms causing changes in cervical function during pregnancy and delivery (12, 13, 15, 18, 26, 27). Apart from the procedure itself, it is postulated that sociodemographic, behavioral, and sexual characteristics of women affected by cervical dysplasia represent an additional risk factor for pregnancy complications (19).

Cervical conization is an established risk factor for cervical insufficiency and consequent preterm delivery (28). The removal of the cervical tissue leads to acquired weakening of the cervix and aberrant synthesis of collagen fibers in regenerated cervical stroma and subsequent reduced tensile strength, which is responsible for its premature dilatation in subsequent pregnancies (18, 29, 30).

Apart from the mechanical role of the cervical mucus plug, the antimicrobial activity of cervical mucus is also impeded by excision of cervical glands (31). Additionally, an insufficient amount of cervical mucus due to cervical glands excision contributes to easier migration of bacteria from the vagina (32). Shortening of the uterine cervix increases the risk of ascending infections and PPROM, chorioamnionitis, and the consequent preterm delivery (13). Nevertheless, literature data indicate that PPROM at <32 weeks of gestation is significantly more frequent in women with prior untreated cervical dysplasia than in general population (21).

The genetic basis for an increased risk of cervical precancer and cancer documented by recent genome-wide association studies indicates a possibility of diminished immune defense to HPV infection (33). This might be true for other infections as well, making these women susceptible to pathogens from the vagina causing chorioamnionitis and rupture of the membranes in pregnancy (30).

Vaginal microbiota (VMB) composition in women with cervical dysplasia is different than that in healthy population. Following cervical excision, VMB composition and levels of proinflammatory cytokines remain unchanged (34). This might account for an increased risk of preterm delivery noticed in women with cervical dysplasia, regardless of whether they were treated or not (21,35). This is the case for their risk of overall (<37 weeks of gestation), severe (<32-34 weeks of gestation), and extreme (<28-30 weeks of gestation) preterm delivery (2). Such a baseline risk could be increased with the treatment sequelae on cervical anatomy and physiology. Cervical microbial diversity is also changed following excision of the cervix, and chorioamnionitis represents one of the complications contributing to an increased risk of preterm delivery after cervical conization (2,35).

Cervical conization impairs local immunity as well (13,21). A decrease in the production of immunoglobulin A as well as lysosomal substances and an increased bacterial reproduction in the cervix and prostaglandin levels in the body observed after conizations could lead to preterm contractions of the uterus and, consequently, to a higher risk of premature labor and premature rupture of membranes (PROM) in patients after conization (36,37,38).

## PREDICTORS OF OBSTETRIC COMPLICATIONS

Defining possible predictors of perinatal complications is essential for modern prenatal medicine. Hence, identifying women who are at risk of complications following cervical treatment is important for providing them adequate surveillance in pregnancy and during delivery.

So far, there are data indicating that the amount of excised tissue, the type of excision, age at treatment, and period after the operation play a role in the occurrence of subsequent maternal complications, perinatal morbidity, and mortality (2,13,21). Apart from the above-mentioned risk factors, repeated excisions represent an additional risk factor for the occurrence of perinatal complications (21). The effect of multiple treatments has been documented to be substantially higher in relation to preterm delivery (2,24).

Surgical techniques of excision associated with removing more tissue are linked to greater risks of perinatal complications (2). Of all conization techniques evaluated in literature, CKC is steadily associated with major perinatal complications (19). Thus, a relative risk of preterm delivery is the highest after CKC, followed by laser conization, and the lowest risk is associated with LLETZ (2.70, 2.11 and 2.02, respectively). The use of CKC is accompanied with excision of more tissue than LLETZ. On the other hand, LLETZ excisions might differ substantially, varying from superficial and low volume excisions to deep and large volume ones (14). In relation to these discrepancies, data on pregnancy complications and outcomes may also exhibit different results. In women who had CKC, there is an additional risk of cervical lacerations during delivery due to grossly changed cervical anatomy and scarring. It has been documented that such injuries are eight times more frequent in these women than in general population (39).

Numerous publications investigated the association between the amount of removed cervical tissue and subsequent obstetric complications, and whether there is a predictive value of cone size in predicting unfavorable perinatal outcomes (2,13,40,41). Both cone volume and height have been investigated, as well as postoperative dimensions of the uterine cervix. Preterm delivery risk increases progressively with increasing cone depth (2,21).

Kyrgiou et al. (13) examined if excised cone dimension correlated with pregnancy duration. They measured pre-treatment and post-treatment dimensions and volume of the cervix using magnetic resonance imaging (MRI), three-dimensional transvaginal sonography (3D-TVS), and two-dimensional transvaginal sonography (2D-TVS) to measure cervical size. The dimensions of the cone and its volume were evaluated before formalin fixation. It was concluded that there were extensive variations in pre-treatment cervical dimensions, and the proportion of the excised tissue amount removed from the cervix correlates with the duration of pregnancy.

Cone height <10 mm provides adequate oncological safety, considering the depth of cervical crypts, and avoids obstetrical harms (5). Conization depth below 10 mm does not increase persistence or recurrence of pathological cytology during a 12-18-month follow-up. Also, HPV infection persistence is not influenced by conization depth below 10 mm during 18 months of postoperative follow-up. Greater depth of excision does not ensure more favorable oncological outcomes, while jeopardizing future reproductive performance. On the other hand, a cone depth >10 mm is associated with a significant increase in the rate of premature delivery, while cone depth >20 mm leads to a five-fold increased rate of premature delivery compared to general population (40). Cone height and gestational age at delivery are significantly correlated (17). This negative correlation is more consistent throughout the literature for cone height than it is for cone volume in relation to preterm delivery (17).

Age younger than 25 years at the time of LLETZ excision represents an independent risk factor for extremely early preterm delivery (before 26 weeks of gestation), regardless of specimen height (42). The association between age at conization, live birth rate and term deliveries was also documented for other types of cervical excisions (43). There are literature data showing that younger women had lower cervical regeneration levels when compared to older women (71%-78% and 89.5%-94.5%, respectively) (44).

Women who conceive within two to three months after the treatment are at an increased risk for preterm delivery (45). After CKC, the incidence of premature rupture of membranes (PROM) has been documented to be higher in pregnancies conceived within six months after the operation than in pregnancies conceived after six months (17). Some reports suggest that pregnancy should be postponed until 12 months upon LLETZ due to increased risk of spontaneous abortion in women who conceived less than 12 months after the procedure (46). According to literature, there is a cervical regeneration deficit, meaning that the average cervical length regeneration is 83.4±10.8% and volume regeneration is 87.4±6.1% six months after the LLETZ procedure (44). Some authors advise postponing pregnancy for at least six months after LLETZ and nine months after CKC (27). Postponing pregnancy after the operation reduces the incidence of perinatal complications, and postoperative contraception is generally recommended for the period of at least six months (17).

Ortoft et al. (21) investigated the effect of two conizations on preterm delivery and perinatal mortality in subsequent pregnancies. The frequency of preterm deliveries was 33% in patients who had had two conizations before pregnancy, and 19% of the children delivered by these women had body weight below 2500 grams. A total of 92% of all spontaneous preterm deliveries in this study were associated with PPROM.

## OVERVIEW OF PERINATAL COMPLICATIONS

The most significant sequel of cervical conization is preterm delivery, frequently associated with PPROM and chorioamnionitis. Nowadays, preterm birth is a major cause of neonatal mortality and morbidity that may be linked to life-long disability. These together cause significant direct and indirect costs for the healthcare system and entire society. Moreover, worries about impaired reproductive performance lead to overall diminished HRQoL in women of reproductive age treated by cervical excision (7,11).

Data on miscarriage rates are inconsistent. While some studies documented increased abortion rates, others found them to be consistent with those of general population (17). So far, there are no data indicating that first trimester miscarriages are more frequent in women who have undergone treatment for cervical dysplasia (30,47). Some publications report increased rates of second trimester abortions and ectopic pregnancies in women treated for cervical dysplasia (30,48).

It has been reported that the rate of cervical cerclage application has increased following conization, and it is higher in women treated with CKC than in those who had LLETZ (2). Its usefulness is controversial and routine prophylactic cervical cerclage is not recommended after CKC (17). Moreover, recently published research found that pregnancies after cervical conization were at an increased risk of preterm delivery, regardless of the prophylactic cerclage placement (49).

Women treated for cervical dysplasia with cervical excision are at an increased risk of preterm delivery, and its rates vary depending on the techniques used, mainly based on the amount of cervical tissue, in particular on the length of the excised cervical canal. Excisional surgery (laser, harmonic scalpel, electric knife) for cervical dysplasia is associated with an increased risk of preterm delivery of up to 25.3%, and this risk is increased before 32 weeks of gestation (49). The incidence of preterm delivery after CKC is also higher than in general population of healthy women (17). A relative risk for delivery before 37 weeks of gestation is the highest after CKC (2.70), followed by laser conization (2.11), whereas LLETZ has the lowest relative risk (1.56) (2). The influence of conization is the same for nulliparous and multiparous women. When comparing women with untreated cervical dysplasia and those who mostly had excisional treatment using LLETZ procedure, preterm delivery reported rates ranged from 3.9% to 11.1%, respectively (21). Frequencies of preterm delivery after cervical surgery vary throughout gestation as follows: 2.9% before 27 weeks, 5.7% between 28 and 31 weeks, 4.0% between 32 and 33 weeks, and 12.7 between 34 and 26 weeks (49). The frequency of preterm delivery in women who had two conizations prior to pregnancy is 33%. Following single excisional treatment, 72% of preterm deliveries start with PPROM; following two excisions, 92% of preterm deliveries start with PPROM (21).

The history of cervical conization has been established as a risk factor for PPROM (50). The reported rate after cervical excision is 13.13% (51). It is more frequent before 31weeks of gestation than between 32 and 36 weeks of gestation (49). The risk of PPROM and chorioamnionitis is higher after CKC than after LLETZ (2). Particularly, the incidence of PPROM is significantly higher in women who underwent CKC six months prior to pregnancy than in those who conceived six months or more after surgery (17). Moreover, when compared to healthy pregnant women, PPROM occurs in significantly earlier gestation in women who underwent CKC (17).

Cervical excision with LLETZ increases the rate of vaginal infections and premature rupture of membranes (PROM) (52). A recently reported frequency of PROM following cervical excision is up to 40% (51).

According to some reports, the CS rate is higher in women who had CKC when compared to healthy women, and it is documented to be as high as 36.4% (17). On the other hand, a recent report, despite having documented a significantly higher incidence of labor dystocia after excisional cervical treatment (15.94%), did not find an increased frequency of CSs in comparison with untreated women (51).

The incidence of neonatal complications has been documented to be significantly higher in women after CKC than in general population and is reported to be as high as 15.4% (17). Perinatal mortality after CKC treatment is significantly increased, while the numbers for laser conization and LLETZ, although increased, failed to reach the level of statistical significance in a meta-analysis published in 2008 (19). Cervical excision significantly increases the incidence of adverse neonatal outcomes, i.e., low birth weight, admission to a neonatal intensive care unit (NICU), and perinatal mortality (2). Recent research documented increased incidence of neonatal intrauterine infectious pneumonia following CKC (17). Perinatal mortality rate following single excisional treatment for cervical dysplasia is 1.0%, mainly in babies delivered before 28 gestational weeks (21).

Heinonen et al. (53) observed an increased risk of premature birth in women who were treated with LLETZ regardless the grade of CIN, and even in patients who did not have CIN lesions. The risk of preterm delivery in this study was 7.2%. The frequency of low-birth-weight neonates was also found to be increased.

Simoens et al. (54) found a significantly increased risk of spontaneous preterm delivery associated with cones more than 10 mm deep when compared to untreated women, while this risk was not significantly increased in case of cones ≤10 mm deep. The corresponding rates of spontaneous preterm deliveries were 20.9% and 8.3%, respectively. These data indicate once again that cones ≤10 mm deep are advisable in women of reproductive age to avoid prenatal complications in subsequent pregnancies. Giving priority to oncological safety in these women might lead to an increased rate of obstetrical adverse outcomes.

## TOPICS FOR FUTURE RESEARCH

There are insufficient data about preventive measures to minimize adverse pregnancy outcomes after conization (47).

A recent meta-analysis evaluated usefulness of transvaginal cervical cerclage in singleton pregnancies following cervical conization (32). A total of nine studies comprising 3560 patients were included, of whom 605 patients had prophylactic cerclage. This research concluded that prophylactic transvaginal cerclage following conization increases the risk of preterm birth and PPROM. These results are in line with a meta-analysis published in 2019, which also concluded that transvaginal cerclage placement in singleton pregnancies following conization did not decrease the rate of preterm births. One of the possible explanations is that braided suture as a foreign body influenced the vaginal microenvironment and the immune system (47). In conclusion, prophylactic transvaginal cervical cerclage increases the risk of preterm birth following conization, which is in line with results published later (49). On the other hand, targeted cerclage using monofilament suture material may reduce the incidence of preterm birth (47). This seems like a reasonable option for women adequately screened using transvaginal ultrasonography with cervical length below 25 mm before 24 gestational weeks. True benefits of such an approach require further investigation (30).

Data on other prospective treatments such as pessary and progesterone use are mainly lacking (48, 55). Data on transabdominal cerclage (TAC) placement are available for patients with extremely short cervix after radical cervical operations and repeated conizations, although some authors reported data on its use in patients after cervical myomectomy and conization for cervical dysplasia (56). Both laparotomic, laparoscopic and robotic approach can be used, and it can be performed during pregnancy and preconceptionally (57). This procedure requires at least two additional surgeries and is not widely used in patients treated with cervical conization, although TAC might present a useful tool in rare cases of deep and/or extensive cervical excisions complicated with cervical insufficiency and when other less invasive procedures have failed (58). In order to proclaim it as safe and feasible for this purpose, further research is required.

## CONCLUSIONS

The association between cervical excisional treatment and perinatal morbidity and mortality is well established. Only a small number of cervical precancerous lesions will progress to invasive cancer. Different excisional treatments are associated with adverse obstetric outcomes and thus, proper management of these changes in women of reproductive age should be based on an adequate selection of women who are at a real risk of developing cervical cancer compared to those who are not at risk. The latter should be protected from overtreatment and its subsequent sequelae. There is evidence that excision of the uterine cervix in women of reproductive age is associated with a small, but real increase in risk of perinatal complications. Excisional treatment should be used only in women with a clear indication and who would benefit from it. Prior to these procedures, all women of reproductive age must be informed about the possible risks of adverse perinatal outcomes linked to excisional treatment of cervical precancerous lesions. Informed consent regarding the treatment must include information about possible long-term adverse effects regarding prenatal complications. Clinicians should be as conservative as possible when treating young women. Treatment of cervical premalignant lesions must be adjusted to minimize possible perinatal adverse outcomes, to provide maximal oncologic safety, and to minimize the rates of residual disease throughout a woman's life.

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# PERINATALNE KOMPLIKACIJE NAKON EKSCIZIONOG LEČENJA CERVIKALNE DISPLAZIJE

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## Sažetak

Karcinom grlića materice predstavlja jedan od od najčešćih malignih tumora u ženskoj populaciji. Masovna primena skringa dovela je do značajnog smanjenja njegove incidencije, uz istovremeni porast incidencije premalignih promena grlića materice. Ove promene se uglavnom dijagnostikuju kod žena u reproduktivnom periodu, kada većina njih nije završila sa reprodukcijom. Osnovni cilj hirurškog lečenja premalignih promena je sprečavanje nastanka karcinoma grlića, uz minimalne rizike po reproduktivnu funkciju.

Najvažnije perinatalne komplikacije su prevremeni porođaj, obično udružen sa prevremenom rupturom plodovih ovojaka i horioamnionitisom. Ovo ima za posledicu prematuritet i rađanje dece niske telesne mase na rođenju, što dovodi do povećanja neonatalnog morbiditeta i mortaliteta. Podaci o učestalosti spontanih pobačaja kod lečenih žena su nekonzistentni, ali se smatra da je učestalost spontanih pobačaja u drugom trimestru povećana.

Kao mogući prediktori pojave komplikacija navode se količina ekscidiranog tkiva, vrsta ekscizione tehnike koja je korišćena, životna dob u trenutku operacije i vreme proteklo od tretmana do začeća. Dodatni faktor rizika za nastanak perinatalnih komplikacija su reekscizije grlića materice. Rizik od perinatalnih komplikacija je najveći nakon konizacije nožem, zatim nakon konizacije laserom, a najmanji nakon ekscizije omčicom, što se prevashodno objašnjava razlikama u veličini konusa. Imajući u vidu da sve premaligne promene grlića materice neće progredirati u karcinom, kao i da su sve vrste ekscizionog tretmana povezane sa povećanjem učestalosti perinatalnih komplikacija, adekvatan pristup podrazumeva pre svega odgovarajuću selekciju pacijentkinja, odnosno lečenje samo onih koje su u realnom riziku od nastanka maligne bolesti. Hirurški pristup mora biti prilagođen tako da obezbedi minimalni rizik nastanka perinatalnih komplikacija, maksimalnu onkološku bezbednost i najmanji mogući rizik rezidualne i/ili rekurentne bolesti tokom života žene.

**Ključne reči:** cervikalna displazija, ekscizija, perinatalni ishod, akušerske komplikacije

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