

# Malformations and Neonatal Problems in Babies of Mothers with Epilepsy: What are the Possible Problems in Women with Epilepsy During Pregnancy?

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## Epilepsi Tanısı Olan Annelerden Doğan Bebeklerde Malformasyonlar ve Neontolojik Sorunlar: Epilepsi Tanısı Olan Kadınların Gebeliği Hangi Sorunlara Gebe?

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### Summary

**Objectives:** The aim of this study was to investigate the effect of epilepsy and its treatment on maternal and fetal outcomes during pregnancy.

**Methods:** The study was designed as a retrospective observational case-control study. One hundred sixty-nine pregnant women (PW) and their newborns were included. The study group consisted of PW with epilepsy (PWWE) (mean age: 27.6 years; n=89), and the control group comprised PW without epilepsy (mean age: 27.5 years; n=80).

**Results:** In the PWWE, unintended pregnancy was found to be higher (p<0.001). Pregnancy complications and cesarean incidence were higher in the PWWE than in the control group. Time of birth was significantly earlier in the PWWE (p<0.01). No significant difference was found between the groups in terms of birth weight, height, sex of infants, and the incidence of birth complications. In the postpartum sixth week visit, all mothers in the control group were nursing their infants, whereas 11.4% of the PWWE weren't nursing their infants (n=10) (p<0.05). During the study, two mothers, and one baby with severe malformation died. The prevalence of major congenital malformations (MCMs) was found as 0% in the drug-free group, 5.7% in the monotherapy group, and 8.3% in the polytherapy group, respectively.

**Conclusion:** Although the majority of the mothers with epilepsy have a healthy pregnancy and healthy baby, we found that the mortality rate and risk of experiencing serious problems in the perinatal and postnatal period were higher compared with the controls. Neonatal disorders and congenital malformations were more common in the infants. It's important that these patients should be followed up closely during the pre-conception, pregnancy, and postpartum periods, and infants should be followed up in tertiary neonatal intensive care units when necessary.

Keywords: Antiepileptic drugs; epilepsy; malformation; newborn; pregnancy.

### Özet

**Amaç:** Epilepsi varlığının ve tedavisinin gebelik boyunca maternal ve fetal sonuçlarının incelenmesi amaçlandı.

**Gereç ve Yöntem:** Çalışma retrospektif gözlemsel vaka-kontrol çalışması olarak tasarlandı. Çalışmaya 169 doğum yapmış kadın ve bu kadınlardan doğan bebekleri alındı. Vaka grubu olarak yaş ortalaması 27.6 epilepsi tanısı olan gebe kadın (n=89) ve kontrol grubu olarak yaş ortalaması 27.5 olan epilepsi olmayan kadın (n=80) dahil edildi.

**Bulgular:** Vaka grubunda istenmeyen gebelik daha fazlaydı (p<0.001). Gebelik komplikasyonları ve sezeryan sıklığı vaka grubunda sağlıklı annelere göre daha fazlaydı. Doğum zamanı vaka grubunda anlamlı derecede daha erkendi (p<0.01). Bebeklerde doğum komplikasyonu sıklığı, cinsiyeti, boy ve kiloları arasında fark saptanmadı. Doğumdan sonraki altıncı hafta kontrolünde kontrol grubundaki annelerin tamamı bebeklerini emzirirken vaka grubunda annelerin %11.4'ü (n=10) bebeklerini emzirmiyordu (p<0.05). Çalışma boyunca epilepsi grubunda 2 anne ve ciddi malformasyonu olan 1 bebek eksitus oldu. Doğum salonunda bebeklerde müdahale gerektirecek neonatolojik sorunlar vaka grubunda daha sıkı. Epilepsi tanısı olan kadınlarda Majör Konjenital Malformasyon (MCM) sıklığı ilaç kullanmayanlarda %0, monoterapi grubunda %5.7, politerapi grubunda %8.3 saptandı.

**Sonuç:** Her ne kadar annelerin çoğunluğu sağlıklı bir gebelik geçirse ve sağlıklı bir bebeğe sahip olsa da bu çok özel hasta grubunda mortalite oranı, perinatal ve postnatal dönemde ciddi sorunların yaşanma riski epilepsisi olmayan kadınlara göre daha yüksektir. Neonatolojik problemler ve konjenital malformasyonlar bu bebeklerde daha sıkıdır. Bu hastaların, prekonsepsiyonel dönemi içerecek şekilde gebelik sırasında yakından takip edilmesi ve bebeklerin gerekli durumlarda üçüncü basamak yenidoğan yoğun bakım ünitelerinde takip edilmesi önemlidir.

Anahtar sözcükler: Antiepileptik ilaçlar; epilepsi; malformasyon; yenidoğan; gebelik.

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## Introduction

One of the most challenging problems in the daily practice of neurologists is deciding whether to use antiepileptic drugs during pregnancy because of the possible negative effects of epilepsy itself on pregnancy and childbirth, as well as the known teratogenic adverse effects of antiepileptic drugs (AEDs). The highest rates of various malformations were reported in polytherapy groups with valproic acid (VPA), and the lowest rates were reported in monotherapy groups with lamotrigine (LTG) and levetiracetam (LEV).<sup>[1-4]</sup>

The incidence of babies with major congenital malformations (MCMs) among women using AEDs is considered to be between 4-8%.<sup>[2,5]</sup> However, considering the possible adverse effects of seizure during pregnancy, it is often not possible to interrupt AEDs during pregnancy.

Women with epilepsy (WWE), who are in the group accepted as high-risk pregnancies, may encounter pregnancy complications more frequently and neonatologic problems such as requirement for resuscitation and admission to neonatal intensive care units are more likely to be encountered in these infants.<sup>[6-8]</sup> The mortality rate of pregnant women with epilepsy is 0.1%, which is 10 times higher than in pregnant women without epilepsy.<sup>[6,7,9]</sup>

The aim of this study was to assess the presence of MCMs, neonatologic problems, and postpartum problems in children of WWE and to compare the findings with children born to women without health problems.

## Materials and Methods

### Case selection and study design

Women who were followed up in the outpatient epilepsy clinic of Ankara Training and Research Hospital were prospectively examined after pregnancy. The diagnosis of epilepsy was confirmed by a neurologist according to the International League Against Epilepsy criteria.<sup>[10]</sup> Folic acid treatment was continued in patients who were started in the preconception period and those who were not taking folic acid were began treatment at the first visit. A total of 5 follow ups were arranged for each woman including each trimester, at birth, and the postpartum sixth week. The babies of age-matched mothers without epilepsy born in the obstetric department of our hospital were included in the control group. The babies in both groups were examined in

detail by a neonatologist twice at birth and at the postpartum sixth week.

Women who were diagnosed as having epilepsy during gestation or less than 1 year before gestation, younger than 16 years, holding a psychiatric diagnosis, using medications other than AEDs, who did not want to participate the study, newborns with incomplete data, and pregnancies resulted in curettage or abortion were excluded from the study. Volunteered women with no history or diagnosis of epilepsy or any other diseases, older than 16 years of age, with no psychiatric symptoms, and who did not take any medication during pregnancy were accepted as control group.

Eighty-nine women with epilepsy (mean age: 27.6 years) and 80 controls (mean age: 27.5 years) were included in the study. Participants in the study and control group were selected among volunteers and informed consent was obtained from each participant. The institutional review board approved the study (27.06.2018/50-511).

### Data capture

Women in both groups completed a questionnaire regarding to their demographic data at the first visit. The frequency and types of seizures, and name and dosage of AEDs used during gestation, gestation complications, screening tests, and ultrasonography results were noted throughout the visits. Timing and type of delivery, presence of complications, and the demographic characteristics of the babies were recorded for both the control and the WWE group. Both groups were followed up postpartum at the sixth week and the mothers were encouraged to breastfeed if they mentioned about negative attitude during the interview. The babies were also examined 6 weeks after delivery for the presence of minor or MCMs. MCMs were identified according to the list reported in the EUROCAT records. MCM was defined as "the presence of surgically, medically, functional, or cosmetically significant malformation that would require serious treatment at birth or within the first 6 weeks after birth."<sup>[2,11]</sup>

### Statistical analysis

Statistical analysis was performed using the SPSS package program (version 20.0; SPSS Inc., Chicago, IL, USA). Data were analyzed using frequency distributions for categorical variables and descriptive statistics for continuous variables, and the results are given as "mean±SD." Malformation ratios were calculated as live birth with malformation+pregnancy

loss with malformation/total live birth+pregnancy loss with malformation. Ninety-five percent confidence intervals were measured using conventional methods.

Normal distribution of data was evaluated using the Kolmogorov-Smirnov test. The independent sample t-test was performed for data with normal distribution as a parametric test ( $p>0.05$ ), and the Mann-Whitney U test was performed for data with abnormal distribution as a nonparametric test ( $p<0.05$ ). The Chi-square test was performed for categorical variables.  $P<0.05$  was considered as statistical significance.

## Results

One hundred sixty-nine women (89 patients and 80 control) with a mean age of 27.55 years and their babies were included in the study. There was no difference between the groups in terms of age and educational status ( $p>0.05$ ). The

demographic data, family history, and backgrounds of the WWE and control groups are given in Table 1.

The frequency of familial epilepsy, febrile convulsions (FC) and congenital malformation was found to be statistically significant in WWE group ( $p<0.05$ ). Planned pregnancy was found to be significantly higher in the control group ( $n=79$ ) than in the WWE group ( $n=42$ ) ( $p<0.001$ ). In the WWE group, among 47 women who had their first babies; only 33 women's first pregnancy, 14 women had abortion history. No difference was observed between the groups in terms of fetal death, neonatal death or spontaneous abortion ( $p>0.05$ ). Eight WWE were treated for infertility before pregnancy; however, all women in the control group conceived spontaneously.

The characteristics of the WWE are summarized in Table 2. Average duration of epilepsy was 10 years; and 44.9% had

**Table 1.** Demographic data of the study and control groups

	Women with epilepsy	Control	p
Age (Mean±SD)	27.6±4.99	27.5±5.44	0.523
Education (n)			0.145
Illiterate	6	11	
≤8 years	50	45	
8–12 years	26	14	
≥12 years	7	10	
Education level of the spouse (n)			0.381
Illiterate	6	6	
≤8 years	47	43	
8-12 years	27	17	
≥12 years	9	14	
Epilepsy in spouse (n) (yes/no)	3/86	1/79	0.351
Consanguineous marriage (n)	7/82	9/71	0.453
Epilepsy history in family (n)	32/57	0/80	<0.001*
Febrile convulsion history in family (n)	14/75	2/78	0.003*
Congenital malformation history in family (n)	18/71	1/79	0.001*
Planned pregnancy (yes/no) (n)	42/47	79/1	<0.001*
Gravida (n)			0.012
Primigravida	33	16	
Multigravida	56	64	
Parity (n)			<0.001*
Primiparous	47	17	
Multiparous	42	63	
The history of stillbirth (n)	4/85	1/79	0.354
The history of neonatal death (n)	3/86	1/79	0.431
The history of spontaneous abortion (n)	20/69	14/66	0.593
Infertility treatment (n)	8/81	0/80	0.005*

SD: Standard deviation.

**Table 2.** The characteristics of the epilepsy in pregnant women with epilepsy

The onset of epilepsy (age), median (interquartile range)	16 (10.5–19.5)
Duration of epilepsy (years), median (interquartile range)	10 (7–16.5)
Type of the epilepsy (n) (focal/generalized)	40/49
Syndrome (n) (juvenile myoclonic epilepsy/juvenile absence epilepsy/Jeavons syndrome)	19/3/1
Epilepsy diagnosis in previous pregnancies (n)	37
The use of antiepileptic drug in previous pregnancies (n)	32
antiepileptic drug (n)	
Not using	8
Monotherapy (TPM/OXB/VPA/CBZ/LTG/LEV)	1/4/8/12/19/25
Polytherapy (without VPA, with VPA)	4/8
Seizure during pregnancy (n)	32
Status epilepticus in pregnancy (n)	1
Seizure during labor (n)	9

CBZ: Carbam-azepine; OXB: Oxcarbazepine; LEV: Levetiracetam; VPA: Valproic acid; LTG: Lamotrigine; TPM: Topir-amate.

**Table 3.** The demographical characteristics of baby and mother

	Women with epilepsy	Control	p
Pregnancy complication (no/yes) (n)	52/37	70/10	<0.001*
Urinary tract infection	10	8	
Gestational hypertension	3	–	
Vaginal bleeding	7	–	
Hyperemesis	11	–	
Risk of premature delivery	4	–	
Preeclampsia	0	1	
Anemia	11	–	
Gestational diabetes mellitus	3	1	
Edema in lowe extremities	3	–	
Deep vein thrombosis	1	–	
Gestational age (weeks)	37.3	39	0.014*
Type of birth (n)			0.002*
Vaginal delivery	32	48	
Cesarean section	56	32	
Delivery complication (n)			0.210
Cephalohematoma	1	–	
Clavicle fracture	1	2	
Difficult birth	3	–	
Sex (n)			
Female/male	40/48	36/44	0.538
Birth weight (g) (mean±SD)	3158 (±472)	3182 (±414)	0.728
Birth height (cm) (mean±SD)	49.07 (±2.17)	49.05 (±1.71)	0.518
Neonatologic problems n (%)	9 (10.3)	4 (5)	108
Minor congenital malformation n (%)	1 (1.1)	2 (2.5)	0.607
Major congenital malformation n (%)	5 (5.7)	0	0.060
Intrauterine death n (%)	2 (2.2)	0	0.498
Maternal death n (%)	2 (2.2)	0	0.498
Breastfeeding (yes/no) (n)	77/10	80/0	0.002*

focal-onset epilepsy. During gestation, patients were followed without medication in 8.9%, monotherapy in 77.5%,

and polytherapy in 13.5%. Thirty two women had at least one seizure during gestation (35.9%), 1 woman had 2 sta-

**Table 4.** Characteristics of babies with neonatologic problems

	Maternal age	AED	Gestational age (weeks)	Sex	Type of delivery	Duration of hospital stay (days)
Apnea	34	Control	37	Female	CS	7
	21	LTG	39	Female	CS	2
	20	LTG	40	Male	Vaginal delivery	4
	24	LTG	38	Female	CS	6
Hypoglycemia	29	CBZ	39	Male	Vaginal delivery	10
	26	CBZ+VPA	41	Male	CS	
Seizure	21	CBZ+LEV+VPA	39	Female	Vaginal delivery	
	30	Control	40	Male	Vaginal Delivery	10
Transient tachypnea of newborn	33	VPA	38	Female	CS	10
	26	LEV	38	Male	CS	7
Meconium aspiration	31	Control	33	Male	Vaginal Delivery	7
Prematurity	20	Control	36	Female	CS	11
Neonatal pneumonia	29	LTG	39	Male	CS	7

CS: Cesarean section; ICU: Intensive care unit.

**Table 5.** Congenital malformations and characteristics

No	Congenital malformation type	Congenital malformation	Sex	Maternal age	Delivery type	Mother	AED	AED dosage during pregnancy mg/d
1	Simian line	Minor	Male	21	Vaginal delivery	Control		
2	Pes equinovarus	Minor	Male	34	Vaginal delivery	Control		
3	Scalp hemangioma	Minor	Male	26	CS	PWWE	LTG	250
4	Congenital hip dislocation	Major	Male	24	CS	PWWE	LEV	1000
5	Microcephaly	Major	Female	26	CS	PWWE	CBZ	600
6	Meningocele	Major	Male	23	CS	PWWE	OXB	600
7	Diaphragm hernias	Major	Female	36	CS	PWWE	LTG	100
8	Fetal valproat syndrome	Major	Male	23	CS	PWWE	VPA	1000

AED: Antiepileptic drug; CS: Cesarean section; PWWE: Pregnant women with epilepsy; LTG: Lamotrigine; Levetiracetam; CBZ: Carbamazepine; OXB: Oxcarbazepine; VPA: Valproic acid.

tus epilepticus, and 9 women had seizures during delivery. Five of the women who had seizures at delivery underwent cesarean section (CS). Pregnancy complications were observed more frequently, the rate of CS was higher in the patient group than the control (Table 3). WWE and control group gave birth at a mean of 37.3 and 39 weeks, respectively and the difference was statistically significant ( $p < 0.05$ ) (Table 3). No significant difference was determined in terms of the frequencies of birth complications, sex distribution, and height and weight of the infants (Table 3). In the postpartum sixth week visit, all mothers in the control group were breastfeeding their infants, whereas 11.4% of

the WWE declined breastfeeding ( $n=10$ ) ( $p < 0.05$ ).

One WWE died due to acute coronary syndrome at 22nd gestation week of pregnancy and the fetus accepted as intrauterine exitus. Another fetal intrauterine exitus was occurred at the 35<sup>th</sup> week of pregnancy in the WWE group. And also a maternal exitus was observed during the postpartum third week, a WWE who had a seizure in the presence of the witnesses and died at home.

Problems observed in infants that needed intervention in the delivery room are shown in Table 4. Four infants had se-

**Table 6.** The number of AEDs and the rate of MCMs in the WWE group

	No medication (n=8)	Monotherapy (n=69)	Polytherapy (n=12)
MCM, n (%)	0 (0)	5 (5.7)	1 (8.3)

AEDs: Antiepileptic drugs; MCM: Major congenital malformations; WWE: Women with epilepsy.

vere apnea, one of which was born from a mother in the control group. The other 3 infants were born from WWE; all were on lamotrigine (LTG).

Congenital malformations detected in the infants are shown in Table 5. In the control group, two different minor malformations in the form of simian line and pes equinovarus were observed, neither of them required surgical or any other interventions. In the patient group, a minor malformation in the form of a hemangioma at the occipitotemporal region was observed in one infant. All MCMs (n=5) were observed in the patient group. They were congenital hip dislocation, microcephaly, meningocele, diaphragm hernia, and fatal valproate syndrome (FVS). The mother of the baby with FVS had status epilepticus twice during her pregnancy and the baby died of sepsis at postpartum third month.

There was no MCM detected in patient group without medication, where it was 5.7% in monotherapy and 8.3% in the polytherapy group (Table 6).

## Discussion

The main result of this study is that neonatal problems were encountered in 10.3% of infants born from women in the WWE and in 5% of the control group. Essentially, it was reported that a small-significant association of epilepsy and neonatological adverse outcomes obtains in pregnancy.<sup>[7]</sup> Similarly, our results indicate that neonatological problems are more common in WWE compared with controls. Apnea was the most frequently observed condition in the infants. Three of the four babies with apnea were born from women with epilepsy, and all three patients were on LTG treatment during their pregnancy. In our opinion, LTG associated with sudden unexpected death in epilepsy (SUDEP) in women with epilepsy may trigger apnea in infants due to intrauterine exposure.<sup>[12]</sup>

Results of our study present that only 33 of the 47 patients with epilepsy who gave birth for the first time, had their first gestation. The difference is due to gestations that resulted

in spontaneous abortion and curettage. Moreover, 52% of pregnancies in the WWE were unplanned pregnancies. These women had to experience the possible complications of their pregnancies. Women with epilepsy who plan to have a baby should be advised to consult a physician in order to take necessary precautions, such as AED regulation and starting folic acid replacement at least three months before conception.

The rate of infertility treatment for pregnancies was determined to be higher in the WWE compared with the control group. Infertility and reproductive disorders were reported to be 2-3 times higher in women with epilepsy.<sup>[13]</sup> Epileptogenic activity may directly stimulate the hypothalamus and hypophysis. Thus, serum levels of prolactin, acute luteinizing hormone (LH), and follicle-stimulating hormone (FSH) increase. Women with epilepsy have lower LH levels, and LH pulse frequency changes compared with healthy women.<sup>[13]</sup> All these hormonal disorders may trigger anovulation and infertility.

Some 1-2% of women with epilepsy are at risk of having tonic-clonic seizures at birth.<sup>[14]</sup> Ten percent of our patients (n=9) had seizures at birth or during the next 24 hours. CS is preferred over vaginal delivery due to the possibility of these women having seizures during childbirth. In fact, 5 of 9 patients who had a seizure in the birth process gave birth by CS. It is known that the rate of CS delivery in women with epilepsy is 2.5 times higher than the normal population.<sup>[6]</sup> CS was more common in WWE compared with the control group due to the maternal choices and the suggestion of the obstetrician. If there is no obstetric obstacle, preferring CS as the delivery method in women with epilepsy does not diminish the possibility of having a seizure; however, it is recommended in selected cases such as in patients with resistant epilepsy, seizures triggered by hyperventilation or who had a seizure in the last trimester.

Maternal mortality and morbidity are increased in pregnant women with epilepsy compared with the general population.<sup>[6,7,11]</sup> It was reported that maternal mortality, pregnancy complications, and neonatologic problems in-

creased 10, 1, and 1.5 times, respectively.<sup>[7,15]</sup> In our study, several complications were observed in 42.5% and 12.5% of WWE and control groups, respectively, and the difference was found as statistically significant. Furthermore, 2 patients (2.2%) died in the course of study. The first patient died of acute coronary syndrome at the 22<sup>nd</sup> week of her pregnancy, and the second patient died after a seizure at the postpartum 3<sup>rd</sup> week. The second patient also had a history of stent placement due to stenosis of the ascending aorta. Comorbid cardiac diseases were apparent in both patients. The maternal mortality rate in pregnant women with epilepsy was reported as high as 0.1% in gestational period.<sup>[9]</sup> However, a much higher rate of 2.2% was observed in our study, which may be due to the presence of major cardiac problems. These patients should be monitored closely during pregnancy due to both pregnancy complications and high maternal mortality rates.

It is well known that AEDs used during pregnancy are associated with structural or cognitive teratogenesis on the fetus.<sup>[16,17]</sup> Although the mechanism of teratogenicity of AEDs has not been clearly elucidated, it was claimed that decreased intrauterine epoxide hydroxylase activity or oxidative damage derived from prostaglandin H synthase bioactivation by AEDs might play a role in teratogenicity.<sup>[18,19]</sup>

Fatal valproate syndrome (FVS) was observed in 1 patient (12.5%) out of our 8 patients on VPA polytherapy, supporting the observation of MCMs being observed at the highest level in polytherapy groups containing VPA.<sup>[20,21]</sup> The other patients in whom MCMs developed in their child were on LEV, CBZ, OXB, and LTG monotherapy. The rate of MCM development in patients on monotherapy was calculated as 5.7%, which was believed to be relatively safer in terms of MCM development. Our data also support previous studies, although our patient number is low.<sup>[1-3,5]</sup> Furthermore, the rate of congenital malformation within the family was higher in the WWE compared with the control group. This increases the possibility of malformations in infants.

Our study results show that non-VPA agents are more likely to be preferred for women of reproductive age among other AEDs. A Dutch study showed that newer AEDs are most often prescribed in children.<sup>[22]</sup> Similarly, it has been reported that the antiepileptic preference has changed for newer antiepileptics in women of childbearing age.<sup>[23]</sup> In

2 previous studies conducted in Turkey in 1992 and 2008, the rates of MCMs in pregnant women with epilepsy were found as 11.5% and 10%, respectively, whereas it was 5.7% in our study.<sup>[24,25]</sup> This may be related to the decreased use of VPA in this group of patients.

In our study, the rate of non-breastfeeding patients in the patient group was found as 11.4%, which was statistically significantly higher than in the control group. It is known that breastfeeding reduces the mother's risk of malignancy and diabetes, as well as many other diseases, including infections, diabetes mellitus, and SUDEP, while strengthening the bond between mother and infant.<sup>[26]</sup> Higher intelligence quotient (IQ) and language scores were reported in infants of breastfeeding mothers on AEDs compared with those whose mothers did not breastfeed.<sup>[27]</sup> Women with epilepsy should be encouraged to breastfeed their babies in the postpartum period.

Our hospital is a tertiary institution to which patients are referred in our region. It is a hospital where high-risk pregnancies are referred and followed up, and complicated cases are seen more frequently. Therefore, we may have encountered riskier situations compared with the normal population in both the study and control groups. This can be considered as a limitation in terms of the generalizability of our study results. We also think that the low number of patients is another limitation of our work.

In conclusion, although the majority of mothers among this very specific group of patients have healthy pregnancies and healthy babies, the mortality rate and risk of experiencing serious problems in the perinatal and postnatal period are higher compared with women without epilepsy. Neonatal disorders and congenital malformations are more common in infants from women with epilepsy. It is important that these patients should be trained in terms of the pre-conception period, and be followed closely during pregnancy and follow-up in tertiary neonatal intensive care units when necessary.

#### **Ethics Committee Approval**

Ethics committee approved.

#### **Peer-review**

Externally peer-reviewed.

#### **Conflict of interest**

The authors declare that they have no conflict of interest.

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