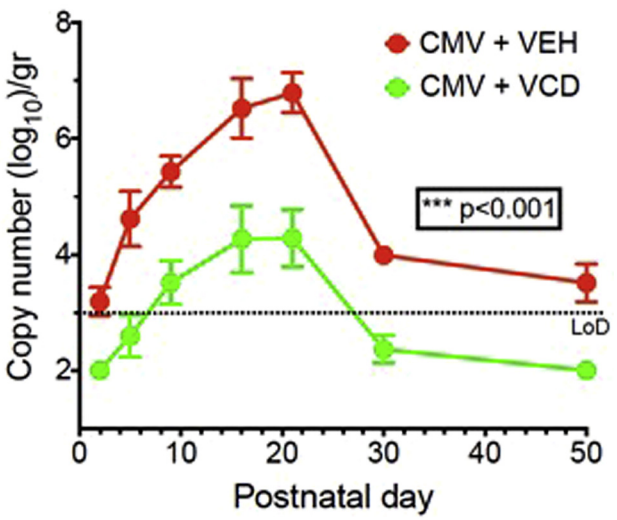
infected fetuses and postnatal therapy is only available for the most severe cases of infection due to substantial safety concerns. We showed that valnoctamide (VCD), a mood stabilizer, effectively blocks CMV. Here we investigate CMV infection in the developing auditory system of newborn mice and the potential benefits of VCD on long-term hearing outcomes.

STUDY DESIGN: Pups inoculated i.p. with CMV (750 PFU) on the day of birth received VCD (n=8) or vehicle (VEH, n=8) daily (1.4mg/mL) from p1 to p21. Brain development of newborn mice parallels that of an early 2nd trimester human fetus. Uninfected animals served as controls (n=8). CMV load and distribution in the cochlea and central auditory regions were assessed by qPCR and histochemistry at multiple time-points post-infection. Hearing was investigated blindly with respect to the experimental group using Auditory Brainstem Responses in 7 week-old mice. Statistical significance was determined by mixed-model ANOVA with repeated measures.

RESULTS: CMV was detected in the cochlea as early as 2 dpi, with viral load peaking at p16-21 and viral particles still measurable at p50. CMV-infected cells were identified in several areas of the inner ear, including the stria vascularis, the temporal bone, and the cochlea, where selective loss of outer hair cells was evident by p12. CMV+ cells were also recognized in central components of the auditory system, such as cochlear nuclei, inferior colliculus, and auditory cortex. Infected mice showed increased hearing thresholds at multiple frequency tone stimuli. VCD substantially reduced CMV load in the cochlea (Fig. 1) and the brain, and ameliorated hearing development with restoration of normal auditory responses (Fig. 2).

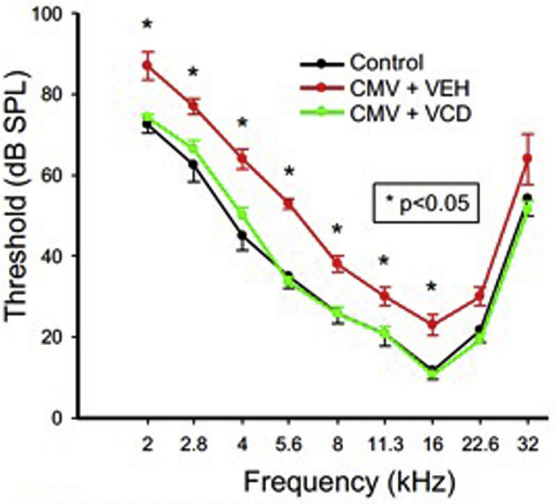
CONCLUSION: VCD effectively blocks CMV infection in the developing auditory system and rescues virally induced hearing impairment. VCD is approved for treatment of neuropsychiatric disorders and lacks teratogenic activity. Thus, it may merit consideration as a novel approach in treating CMV-mediated deafness during development.

Fig. 1. VCD suppresses CMV load in the cochlea.



LoD, limit of detection.

Fig. 2. Auditory responses in 7 week-old mice.



dB SPL, decibel sound pressure level.

6 The impact of the HYPITAT I trial on obstetric management and outcome for gestational hypertension and preeclampsia in the Netherlands

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OBJECTIVE: In 2009, the HYPITAT I study showed that in women with pregnancy induced hypertension or preeclampsia at term, induction of labor reduces maternal morbidity compared with expectant management, without compromising neonatal outcome or cesarean section rate. We aimed to evaluate the impact of the HYPITAT I trial results on obstetric management and subsequent maternal and neonatal outcomes in the Netherlands, five years after the trial, as compared to before the trial.

STUDY DESIGN: We studied aggregated data from the Dutch National Perinatal Registry from 2000 to 2014. We studied women with hypertension in pregnancy or preeclampsia and a singleton fetus in cephalic position between 36 to 41 weeks' gestation. Outcome measures were induction of labor, mode of delivery and the occurrence of maternal and neonatal complications. We compared the proportions of the period before the trial (2000-2005) to the period after the trial (2008-2014). We also compared outcomes to a reference group of women without hypertensive disorders in pregnancy.

RESULTS: We evaluated data of 55 780 women before to 70 890 after the trial (Table 1). Induction of labor increased from 51.1% to 64.2% (RR 1.26 (95 %CI 1.24-1.27)). This increased rate was more pronounced in HYPITAT I participating hospitals compared to non-participating hospitals (participating: 48.5% to 64.5% (RR 1.33; 95% CI 1.31-1.35); non-participating: 53.4% to 63.9% (RR 1.20; 95% CI 1.18-1.21)). A reduction was observed in the instrumental delivery rate after the trial compared to the period before the trial (16.5% to 13.1%; RR 0.79; 95% (CI 0.77-0.81)). Spontaneous delivery rates

slightly increased from 65.0% to 66.7% (RR 1.03 (95%CI 1.02-1.04)). Emergency caesarean section rates were 12.8% and 14.4% respectively (RR 1.12; 95% (CI 1.09-1.16)). Maternal mortality ratio reduced from 3.5 to 1.2 per 100 000 live births. Perinatal death reduced from 0.49% to 0.27% (RR 0.54 (95% CI 0.45-0.65)). The reduction in perinatal mortality over time was greater in women with hypertension compared to women without hypertensive disorders (Figure 1).

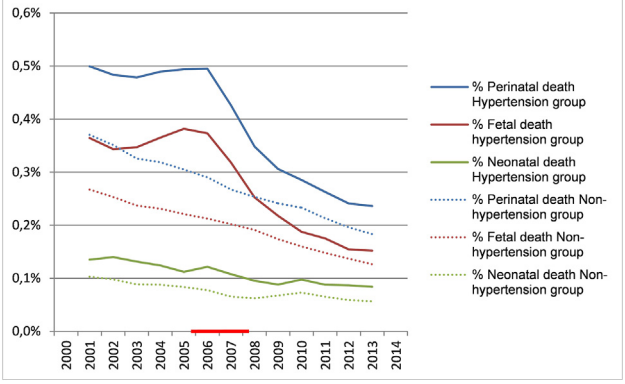
CONCLUSION: HYPITAT I lead to an increased induction of labor rate in women with a hypertensive pregnancy at term. This was associated with significant reductions in maternal morbidity and mortality, and perinatal mortality.

Table 1. Outcomes in pregnancies complicated by pregnancy induced hypertension or preeclampsia between 36 and 41 weeks' gestation before, during or after the HYPITAT I trial.

	Before 2000-2005 (n=55,780)	During 2006-2007 (n=17,079)	After 2008-2014 (n=70,890)	Relative Risk (95% CI)	P-Value
All women (n=143,749)					
Onset of labor [a]					
Spontaneous	24002 (43.1%)	7429 (43.6%)	20639 (29.8%)	0.69 (0.68-0.70)	p<0.001
Induction of labor	28451 (51.1%)	8577 (50.3%)	44447 (64.2%)	1.26 (1.24-1.27)	p<0.001
Elective CS	3214 (5.77%)	1037 (6.08%)	4135 (5.97%)	1.02 (0.99-1.08)	p=0.136
Mode of Delivery [b]					
Spontaneous	36197 (65.0%)	11138 (65.3%)	47124 (66.7%)	1.03 (1.02-1.04)	p<0.001
Instrumental delivery	9184 (16.5%)	2523 (14.8%)	9218 (13.1%)	0.79 (0.77-0.81)	p<0.001
Elective SC	3214 (5.77%)	1037 (6.08%)	4135 (5.85%)	1.02 (0.97-1.06)	p=0.514
Emergency SC	7133 (12.8%)	2361 (13.8%)	10161 (14.4%)	1.12 (1.09-1.16)	p<0.001
Maternal complications					
Diast BP > 110 mmHg [c]	11484 (20.6%)	3243 (19.0%)	8528 (12.1%)	0.59 (0.57-0.60)	p<0.001
Eclampsia	193 (0.35%)	21 (0.12%)	34 (0.05%)	0.14 (0.10-0.20)	p<0.001
HELLP	805 (1.44%)	230 (1.35%)	706 (1.00%)	0.69 (0.62-0.76)	p<0.001
PPH>1L[d]	2888 (5.34%)	1181 (7.22%)	5652 (8.13%)	1.52 (1.46-1.59)	p<0.001
Placental abruption	106 (0.19%)	17 (0.10%)	47 (0.07%)	0.35 (0.25-0.49)	p<0.001
Maternal infection	86 (0.15%)	14 (0.08%)	115 (0.16%)	1.05 (0.80-1.39)	p=0.721
Neonatal complications					
Neonatal infection	430 (0.77%)	99 (0.60%)	529 (0.75%)	0.97 (0.85-1.10)	p=0.615
Apgar 5 min < 7 [e]	1045 (1.87%)	304 (1.78%)	1291 (1.82%)	0.97 (0.90-1.05)	p=0.491
Perinatal Death	276 (0.49%)	82 (0.48%)	190 (0.27%)	0.54 (0.45-0.65)	p<0.001
• Fetal Death	203 (0.36%)	60 (0.35%)	128 (0.18%)	0.50 (0.40-0.62)	p<0.001
• Neonatal Death	73 (0.13%)	22 (0.13%)	62 (0.09%)	0.67 (0.48-0.94)	p=0.019

Data are in number of patients and proportions without missings (%). The years between 2000 and 2014 were distinguished in the period before trial (2000-2005), the period during trial (2006, 2007) and the period after trial (2008-2014). Chisquare tests were used to calculate statistical difference of the proportions without missing values between the before and after trial group. Elective SC = elective cesarean section. Emergency SC = emergency cesarean section. Diast BP > 110 mmHg = diastolic blood pressure > 110 mmHg. HELLP = hemolysis, elevated liver enzymes and low platelet count. PPH = postpartum hemorrhage. [a]= 113 missings before, 36 missings during, 1669 missings after trial. [b]= 52 missings before, 20 missings during, 252 missings after trial. [c]= 18 missings before, 6 missings during, 456 missings after trial. [d]= 1741 missings before, 728 missings during, 1339 missings after trial. [e]= 16 missings before, 7 missings during, 15 missings after trial.

Figure 1. Perinatal-, fetal and neonatal death in the Hypertension group versus Non-hypertension group (3 year moving average)



7 Maternal administration of melatonin for prevention of preterm birth and fetal brain injury associated with premature birth in a mouse model

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OBJECTIVE: Many studies have suggested that intrauterine infections may be a cause of preterm birth. Melatonin exhibits immunomodulatory effects in many inflammatory conditions. We hypothesized that melatonin may decrease the rate of preterm birth and protect fetal brain through changes in the anti-inflammatory and regulatory milieu.

STUDY DESIGN: A mouse model was used with the following groups: (1) control; (2) LPS group, inflammation by an intraperitoneal(IP) injection of lipopolysaccharide (LPS); and (3) LPS with melatonin group, IP injection of LPS and pretreatment with melatonin at E17. Inflammation was analyzed in the uterus, placenta, and fetal brain using real-time RT-qPCR or immunohistochemistry. Immunofluorescent staining was used to examine the morphological condition of neurons in fetal brain. We performed western blotting to characterize the expression and activity of silent information regulator transcript-1 (SIRT1) and nuclear factor-erythroid 2-related factor 2 (Nrf2) in uterine strips.

RESULTS: Melatonin decreased the rate of preterm birth compared with that in the LPS group (30 vs. 100%, $P<0.01$). Latency period from LPS injection to delivery was longer in LPS with melatonin group than LPS group(42 vs. 10h, $P<0.01$). Coadministration of melatonin was associated with decreased proinflammatory cytokines in the uterus and placenta. In LPS group, layers of the fetal brain are indistinguishable (fig. 1C) and polarity of normal migration of neuroblasts was destroyed. Cortical plate became thinner and neutrophils were seen (fig. 1D). In LPS with melatonin group, all layers of the cortex maintain well (fig. 1E). Neuronal differentiation is accelerated in the cortical plate (fig. 1F). Melatonin inhibited LPS-induced neurotoxicity (fig. 2; cortical neuronal primary culture). Western blot analysis in the uterine strips showed that relative integrated densities for SIRT1 and Nrf2 were increased significantly in the melatonin group, compared with other groups ($P<0.05$).

CONCLUSION: Maternally administered melatonin appears to modulate the maternal and fetal immune response to intrauterine inflammation and decreases the frequency of preterm birth and fetal brain injury. Current results suggest that melatonin could be a new therapeutic agent to prevent preterm birth and fetal brain injury.