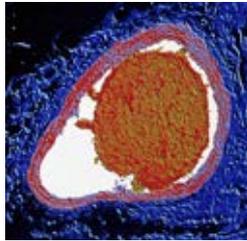


research



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Spontaneous vaginal birth with epidural more likely when laying down in 2nd stage labour p104

ORIGINAL RESEARCH Multicentre, population based, observational study

Comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism

Jun M, Lix LM, Durand M, et al
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 Find this at: <http://dx.doi.org/10.1136/bmj.j4323>

Study question How safe is direct oral anticoagulant (DOAC) use compared with warfarin use for the treatment of venous thromboembolism?

Methods This was a retrospective, propensity score matched cohort study conducted between 1 January 2009 and 31 March 2016 using healthcare data from six jurisdictions in Canada and the United States. The study cohort included adults aged 18 years or over with a new diagnosis of venous thromboembolism and a prescription

for a DOAC (apixaban, dabigatran, or rivaroxaban) or warfarin within 30 days of diagnosis. The primary outcome was an incident major bleed within 90 days after the start of treatment. Propensity score matching and shared frailty models were used to estimate adjusted hazard ratios and 95% confidence intervals of the outcomes. Analyses were conducted independently at each site, with meta-analysis used to estimate pooled hazard ratios across sites.

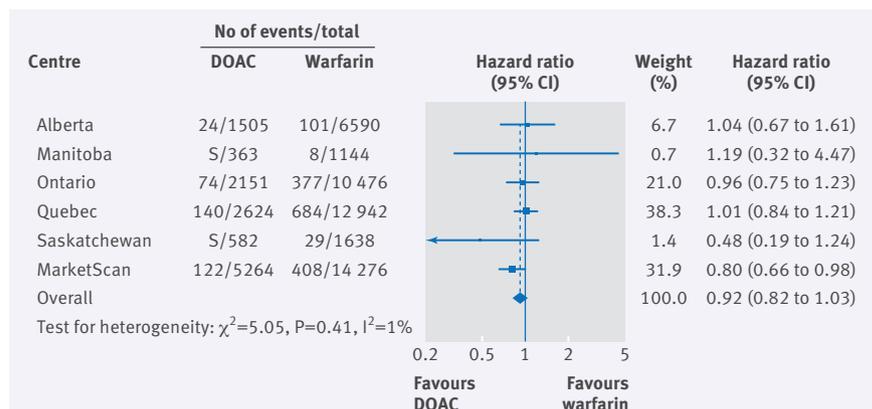
Study answer and limitations

Among 59 525 adults (12 489 DOAC and 47 036 warfarin users), 1967 (3.3%) had a major bleed and 1029 (1.7%) died over a mean follow-up of 85.2 days. The overall risk of major bleeding was similar for DOAC compared with warfarin use (hazard ratio 0.92, 95% confidence interval 0.82 to 1.03).

Owing to the observational study design, the possibility of residual confounding arising from differences in unmeasured variables remains.

What this study adds This study, which represents the largest multicentre, population based assessment of the safety of DOACs compared with warfarin among patients with a new diagnosis of venous thromboembolism, suggests that DOAC use is not associated with higher risk of major bleeding.

Funding, competing interests, data sharing This study was conducted by the Canadian Network for Observational Drug Effects Studies (CNODES), funded by the Canadian Institutes of Health Research. CW has received honorariums from Leo Pharma and Pfizer, and SMM has received research grants for work unrelated to this project from GlaxoSmithKline, Merck, Pfizer, and Sanofi. Trial registration ClinicalTrials.gov NCT02833987.



Hazard ratios (95% CIs) of major bleeding associated with direct oral anticoagulant (DOAC) use compared with warfarin use (reference category was warfarin users). S=events were <5 and cells were suppressed

New cerebral findings in infants with Zika syndrome

ORIGINAL RESEARCH Case series study

Follow-up brain imaging of 37 children with congenital Zika syndrome

Petribu NCdL, Aragao MdFV, van der Linden V, et al
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Find this at: <http://dx.doi.org/10.1136/bmj.j4188>

Study question Are there differences in cerebral calcifications between initial and follow-up computed tomography (CT) scans in children with congenital Zika syndrome?

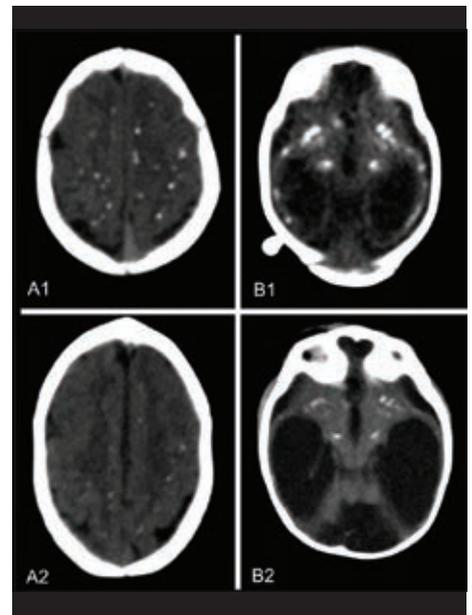
Methods A case series study using convenience sampling in 37 children with congenital Zika syndrome during the microcephaly outbreak in Pernambuco, Brazil (2015), who underwent brain CT shortly after birth and at one year follow-up.

Study answer and limitations All children had cerebral calcifications on the initial scan, predominantly at the cortical-white matter

junction. At follow-up scan the intracranial calcifications had diminished in number, size, or density, or a combination in 34 of the children (92%, 95% confidence interval 79% to 97%), were no longer visible in one child, and remained unchanged in two. No child showed an increase in calcifications. These imaging changes were not associated with any clear clinical improvements. One limitation of this study was the subjective quantification of cerebral calcifications.

What this study adds The detection of cerebral calcifications should not be considered a major criterion for late diagnosis of congenital Zika syndrome, nor should the absence of calcifications be used to exclude the diagnosis.

Funding, competing interests, data sharing The study received no external funding. See bmj.com for competing interests. Initial and follow-up CT images, clinical data, and statistical calculations are available from the corresponding author.



CT brain scans after birth (A1 and B1) and at one year follow-up (A2-B2) in two children with Zika syndrome, showing diminished number, size, or density of calcifications

COMMENTARY Calcification that resolves sets Zika apart from other congenital infections

In this issue, Petribu and colleagues report new and important findings in the central nervous system on follow-up computed tomography (CT) scans from a series of 37 infants with confirmed or probable congenital Zika syndrome.⁶

They found a surprising decrease in the overall number and size of subcortical calcifications at one year follow-up, which did not correlate with the degree of cerebral volume loss. Calcifications reduced in 34 infants, and, remarkably, disappeared altogether in one. These findings suggest that the sequelae of this strain of congenital Zika virus may be different from those of most other congenital infections in which bulky calcifications are often permanent.

The authors' longitudinal prospective study design allows within person comparison of neuroimaging findings and helps characterise the clinical course of congenital Zika syndrome, at least with respect to the appearance of cerebral pathology on non-invasive imaging.

These findings may be specific to the particular strain of Zika virus found in this region of Brazil

However, there at least three important caveats to consider. Firstly, this is a relatively small case series of just 37 infants, and confirmation is required. Secondly, these findings may be specific to the particular strain of Zika virus found in this region of Brazil, so the generalisability of the findings is unclear. Finally, as the authors state, none of the infants had follow-up magnetic resonance imaging scans, which limits a more detailed evaluation of the structural changes that may have occurred during follow-up.

The authors report an intriguing hypothesis for their findings, informed by histological analyses of autopsy specimens from fetuses who died during different Zika outbreaks in Slovenia and Washington, DC in the US. The specimens showed no evidence of inflammatory histological changes.^{7,8} Laboratory research in human cells and animal models also supports a non-inflammatory pathological mechanism of neuronal loss after Zika infection, and

the authors hypothesise that the process involves non-inflammatory induced apoptosis of neuroprogenitor cells followed by phagocytosis by microglia (the brain's scavenger cells). The authors propose that calcium deposits are reduced by the same phagocytic process.

The pathophysiological hypothesis of Petribu and colleagues should encourage further research into the target cells affected and host's immune responses after gestational infections with the Brazilian strain of Zika virus. Their description of decreasing or complete resorption of calcifications in affected infants suggests that this imaging characteristic may be what sets congenital Zika syndrome apart from other congenital infections. Any implications for clinical improvement remain unclear.

For now, the most important conclusion from this study is that absence of subcortical calcifications on non-invasive neuroimaging should not be used to rule out a diagnosis of congenital Zika syndrome.

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Incidence, clinical management, and mortality risk following self harm among children and adolescents

Morgan CM, Webb RT, Carr MJ, et al

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Find this at: <http://dx.doi.org/10.1136/bmj.j4351>

Study question What are the temporal trends for sex and age specific incidence of self harm in children and adolescents, and what are the clinical management trajectories and cause specific mortality risks following an initial self harm episode?

Methods A population based cohort study using the Clinical Practice Research Datalink (CPRD) identified 16 912 young people aged 10-19 years who harmed themselves during 2001-14. Temporal trends for sex and age specific annual incidence rates were examined, and the likelihood of referral to mental health services and psychotropic drug prescribing patterns were assessed. The authors linked children and adolescents from eligible English practices (n=8638) to hospital episode statistics and Office for National Statistics mortality records and matched them by age, sex, and general practice with up to 20 unaffected children and adolescents (n=170 274). Stratified Cox proportional hazards models were used to estimate relative risks of all cause mortality, unnatural death, and fatal acute alcohol or drug poisoning.

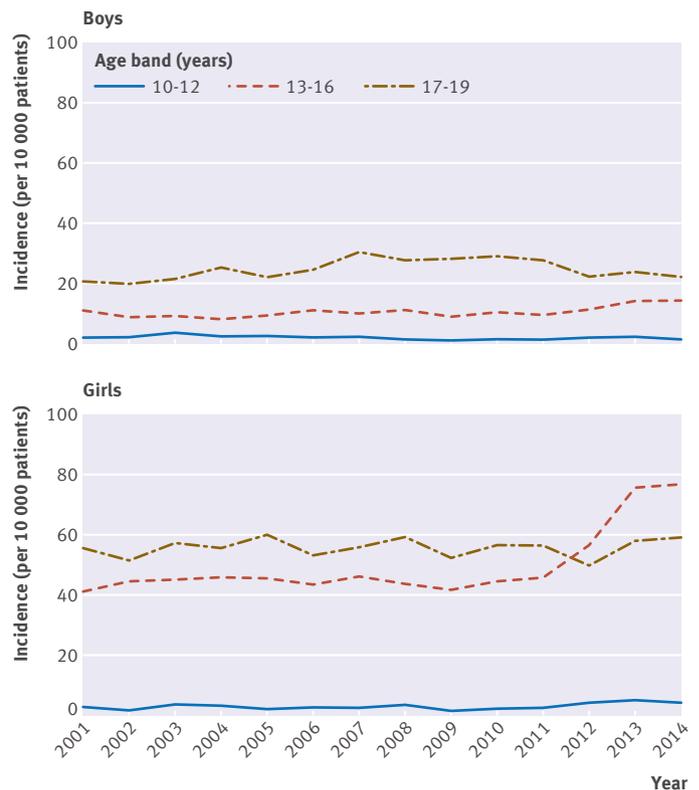
Study answer and limitations Annual incidence rates were increased in girls compared with boys (37.4 v 12.3 per 10 000) with a particularly sharp 68% increase in incidence among girls aged 13-16, from 45.9 to 77.0 per 10 000 between 2011 and 2014. Referrals within 12 months following self harm were 23% less likely for young patients registered at the most socially deprived practices. Children and adolescents who harmed themselves had especially noticeable increases in risks compared with unaffected matched peers for dying by suicide (deprivation adjusted hazard ratio 17.5, 95% confidence interval 7.6 to 40.5) or by acute alcohol or drug poisoning (34.3, 10.2 to 115.7).

What this study adds The possible recent increase in incidence of self harm among mid-teenage girls represents a societal concern. The likelihood of referral was lowest in practices in the most deprived localities where incidence was highest—an illustration of the “inverse care law.” Increased risks of suicide and fatal alcohol or drug poisoning highlight the importance of effective interagency collaboration.

Funding, competing interests, data sharing National Institute for Health Research through the Greater Manchester Primary Care Patient Safety Translational Research Centre (grant No GMPSTRC-2012-1). Data from CPRD cannot be shared because of licensing restrictions.



GRAHAM CLARK/ALAMY



Temporal trends in annual age specific self harm incidence stratified by sex. Standardised by index of multiple deprivation fifth and region of residence



APHP-COCHIN-VOISIN/PHANIE/SPL

Upright versus lying down position in second stage of labour in nulliparous women with low dose epidural

The Epidural and Position Trial Collaborative Group

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Find this at: <http://dx.doi.org/10.1136/bmj.j4471>

Study question Does an upright position in the second stage of labour in nulliparous women with a low dose epidural increase the chance of spontaneous vaginal birth compared with lying down?

Methods Randomised controlled trial recruiting nulliparous women at term with a singleton cephalic presentation, in second stage labour with epidural analgesia. Allocation was to an upright or a lying down position with no masking of participants or clinicians. The primary outcome was spontaneous vaginal birth. An intention to treat analysis was performed.

Study answer and limitations Statistically significantly fewer spontaneous vaginal births occurred in women in the upright group: 35.2% (548/1556) compared with 41.1% (632/1537) in the lying down group (adjusted relative risk 0.86, 95% confidence interval

0.78 to 0.94). For most of the secondary maternal, neonatal, or longer term outcomes there was no evidence of differences. This study could not be masked so results may be influenced by women's and midwives' perceptions of the different positions in their ability to achieve a spontaneous vaginal birth. Existing guidance recommends that women should be encouraged to be upright, so we might expect this position to suggest an improvement in spontaneous vaginal births. The finding that lying down increased the chances of achieving a spontaneous vaginal birth suggests that this potential bias was either absent or minimal in its impact.

What this study adds In nulliparous women with a singleton fetus and an epidural in labour at term, lying down (left or right lateral) during the second stage of labour increases the chance of spontaneous vaginal birth compared with being upright.

Funding, competing interests, data sharing This project was funded by the National Institute for Health Research health technology assessment programme (project No 08.22.02). The authors have no competing interests. Requests for access to data from the Birth in the Upright Maternal Position with Epidural in Second stage (BUMPES) trial should be addressed to the corresponding author.

Study registration Current Controlled Trials ISRCTN35706297.

Primary and selected secondary short term outcomes			
Outcomes	No (%)		Adjusted* risk ratio (confidence interval)
	Upright (n=1556)	Lying down (n=1537)	
Primary outcome			
Spontaneous vaginal birth	548 (35.2)	632 (41.1)	0.86 (0.78 to 0.94)
Key short term secondary outcomes			
Instrumental vaginal delivery†	849 (54.6)	778 (50.6)	1.08 (0.99 to 1.18)
Forceps delivery	578 (37.2)	503 (32.7)	
Ventouse delivery	271 (17.4)	275 (17.9)	
Caesarean section‡	158 (10.2)	127 (8.3)	1.23 (0.92 to 1.64)
Episiotomy performed	914 (58.8)	838 (54.6)	1.07 (0.99 to 1.16)
Perineal tear evident (including perineal tear with episiotomy)	759 (48.9)	785 (51.1)	0.95 (0.87 to 1.04)
Obstetric anal sphincter injury§	104 (6.7)	81 (5.3)	1.27 (0.88 to 1.84)
Neonatal resuscitation at birth	206 (13.3)	180 (11.7)	1.13 (0.89 to 1.44)
Neonatal admission to higher level of care¶	108 (7.0)	96 (6.3)	1.11 (0.79 to 1.56)

*Adjusted for centre as a random effect.
 †Compared with no instrumental vaginal delivery.
 ‡Compared with no caesarean section.
 §Severity grades 3 and 4.
 ¶Includes transitional care.

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