MADRAC Bulletin

For healthcare professionals only
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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

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Articles Based on Case Reports

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What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report article(s).

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that health care providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not exhaustive but rather represents a selection of clinically relevant items that warrants dissemination.

Superior Sagittal Sinus Thrombosis following Combined Oral Contraceptives Use: A Rare but Serious Adverse Drug Reaction

By Nur Ayuni binti Ahmad

Case Report[1]

A 52-year-old female patient with no known medical illness had been taking a combined oral contraceptive (COC) pill containing levonorgestrel/ethinylestradiol (LNG/EE) for 14 years. She presented with sudden left-sided weakness involving both upper and lower limbs, numbness, and inability to ambulate. She reported a history of chronic headache, particularly during menstruation, but had no facial asymmetry, speech disturbances, or visual symptoms.

On admission, an initial computed tomography (CT) brain showed acute intraparenchymal haemorrhage at the right frontoparietal region with marked perilesional oedema, mild midline shift and compression of the right occipital horn and body of the right lateral ventricle. A cord sign suggestive of **superior sagittal sinus thrombosis** (SSST) with hyperdense cortical veins was observed. A repeat CT scan the following day confirmed extensive cerebral venous sinus thrombosis involving the superior sagittal sinus (from vertex to torcula), left transverse sinus, sigmoid sinus and left internal jugular vein, with the straight sinus remaining patent.

AI-generated image

LNG/EE was discontinued. The patient underwent urgent right decompressive craniectomy, followed by anticoagulation and antiepileptic therapy, including enoxaparin, dabigatran, phenytoin and levetiracetam. Follow-up imaging showed stable intraparenchymal haemorrhage with persistent perihaemorrhagic oedema and sulcal effacement.

The patient gradually improved neurologically with physiotherapy and occupational therapy. She was discharged with dabigatran and antiepileptic medications, with outpatient follow-up in neurosurgery and rehabilitation clinics. Considering the temporal relationship and the established thrombotic risk of LNG/EE, the adverse event was assessed as *possibly* related to the drug.

Discussion

Levonorgestrel/ethinylestradiol (LNG/EE) is a second-generation combined oral contraceptive containing a fixed-dose combination of synthetic progestogen and oestrogen.[2] Its contraceptive effects result from three complementary actions which include inhibition of ovulation through the hypothalamic–pituitary axis, thickening of cervical mucus to impede sperm penetration, and endometrial changes that prevent implantation. Currently, there are six LNG/EE-containing products registered in Malaysia, all available in tablet form.[3]

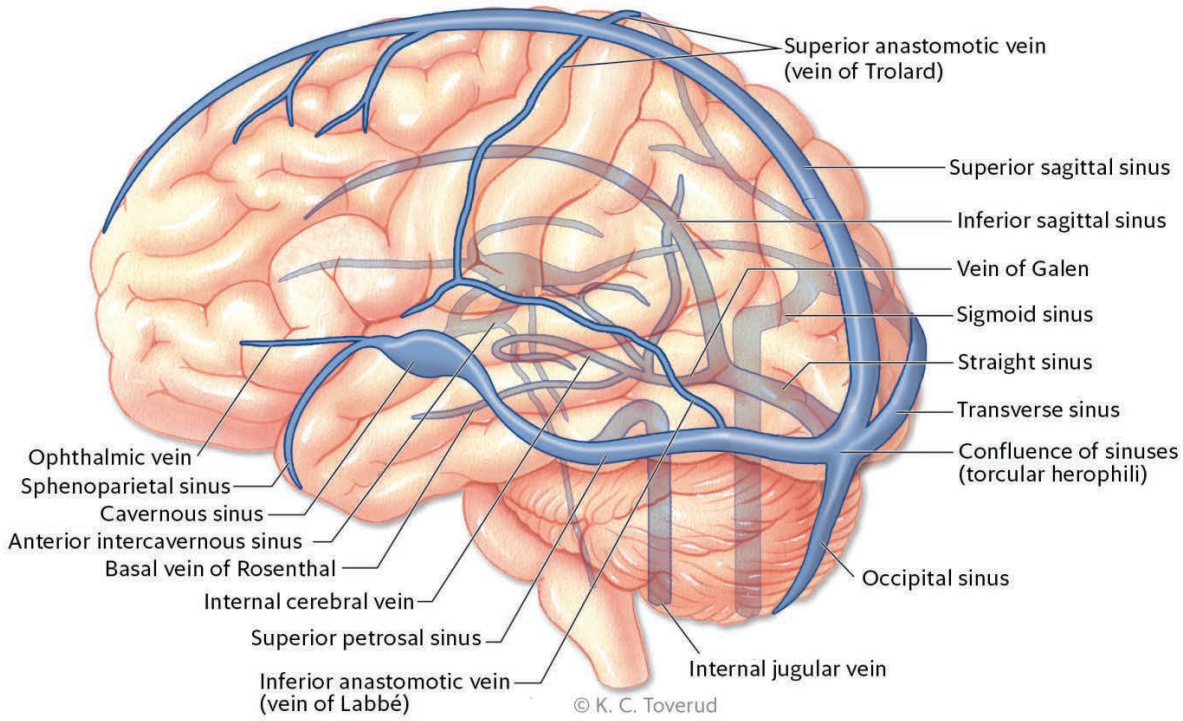

Figure 1: Overview of cerebral venous system[9]

Superior sagittal sinus thrombosis (SSST) is a subtype of cerebral venous sinus thrombosis (CVST) within the spectrum of venous thromboembolism (VTE).[4] It is rare condition in which thrombosis of the dural venous sinuses obstructs the cerebral venous drainage, with the superior sagittal sinus being the most commonly affected site.[4,5] Impaired cerebral venous drainage can result in raised intracranial pressure, venous infarction, and intracerebral haemorrhage. The most common symptom is a persistent headache, typically diffuse or generalised that often resembles a migraine or a sudden "thunderclap" headache. Other clinical manifestations include seizures, focal neurological deficits such as hemiparesis or aphasia, and papilledema or visual disturbances. In severe cases, altered consciousness, brain herniation or coma may occur. SSST is the most frequent form of CVST, accounting for 0.5% to 1% of all strokes and predominantly affecting women of reproductive age.[5]

The pathophysiology of SSST associated with LNG/EE use is likely multifactorial.[6] The oestrogen component increases plasma concentrations of coagulation factors, including factors II, VII, VIII, X, and fibrinogen, while reducing natural anticoagulants such as antithrombin III, protein S, and tissue factor pathway inhibitor, resulting in a hypercoagulable state.

LNG/EE has a rare but well-documented association with VTE.[2,6,7] VTE commonly presents as deep vein thrombosis or pulmonary embolism; however, thrombosis has been reported extremely rarely in other blood vessels, including the cerebral, hepatic, mesenteric, renal, or retinal veins and arteries in contraceptive pill users.[2] The estimated annual incidence of CVST in the general population is low, ranging from 3-4 cases per million; however, the use of LNG/EE significantly increases this risk.[2,5,6,7] The risk is further elevated in women with additional risk factors, including obesity, age over 35 years, major surgery with prolonged immobilisation, a personal or family history of thrombosis, smoking and inherited thrombophilia.[2,6,7] The risk of thrombotic events is highest during the first year of LNG/EE initiation, particularly within the first three to six months. One study reported that the average duration of COC use prior to a thromboembolic complication was 13.6 months.[6] Furthermore, the risk is renewed when treatment is restarted after a break of four weeks or more.[2,6,7]

Management of SSST requires immediate discontinuation of LNG/EE, urgent stabilisation of increased intracranial pressure and seizures, and the initiation of anticoagulation therapy.[2,5] Switching to non-oestrogen-based contraception, such as progestogen-only pill or intrauterine devices should also be considered.[5]

To date, the National Pharmaceutical Regulatory Agency (NPRA) has received 98 local adverse drug reaction (ADR) reports involving 173 adverse reactions suspected to be associated with LNG/EE.[1] The most frequently reported adverse events include urticaria (23 reports), pruritus (12), and headache (10). At the time of writing, **one local case of SSST associated with LNG/EE** use has been reported, as described above. In addition, five other thromboembolic events were reported locally, including three cases of deep vein thrombosis and two cases of pulmonary embolism. All cases occurred in female patients aged 28 to 49 years. Two patients recovered, while the outcome of the remaining cases were unknown. As of January 2026, the World Health Organisation (WHO) database has recorded 2 global reports of SSST and 25 reports of CVST associated with LNG/EE.[8]

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

AI-generated image

Advice for Health Care Professionals

• **Assess** patients' medical and family history before initiating or restarting LNG/EE and **avoid** its use in women with current or previous VTE, known hereditary or acquired thrombophilia, major surgery with prolonged immobilization, or multiple risk factors such as obesity and age above 35.

• **Monitor** patients closely, particularly during the first year of use or after restarting LNG/EE following a treatment interruption of ≥4 weeks.

• **Educate** patients to seek immediate medical attention if they develop symptoms suggestive of CVST/SSST such as severe or prolonged headache, seizures or loss of consciousness, sudden vision changes, or numbness or weakness in the face, arm or leg, especially on one side.

• **Discontinue** LNG/EE immediately if SSST is suspected or confirmed, and **switch** to a non-oestrogen-based contraception such as progesterone-only pill or intrauterine device.

• **Report** all suspected adverse drug reactions associated with LNG/EE-containing products to the NPRA.

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Features

Internal Workshop on Pharmacovigilance Case Report Writing

On 11 March 2026, the Pharmacovigilance Section of the National Pharmaceutical Regulatory Agency (NPRA) organised an internal workshop on pharmacovigilance case report writing. The workshop aimed to strengthen officers' skills in writing clear, structured, and evidence-based pharmacovigilance articles, while demonstrating how artificial intelligence (AI) tools can support efficient drafting.

The first session was the theory component of the workshop, where key concepts in pharmacovigilance case report writing were introduced. Participants learnt about the purpose of such articles in communicating safety information to healthcare professionals, the differences between safety reviews, safety alerts and case report articles, and the importance of maintaining clarity, accuracy, and credibility in regulatory publications. The responsible use of AI tools in literature search and scientific writing was also discussed, emphasising that while AI can support drafting, human oversight remains essential particularly when conducting literature review or critical appraisal of evidence.

Following the theory session, officers involved in article writing continued with a hands-on training session. Participants applied the principles discussed earlier to draft a pharmacovigilance case report using a structured framework. The use of AI tools was practised during the writing process, including Consensus, Gemini, and Felo for reference search and cross-checking; NotebookLM for summarising documents; ChatGPT for refining drafts; and Mendeley Cite for in-text citation and bibliography generation. These tools enhanced writing efficiency while ensuring scientific content remained accurate and evidence-based.

The knowledge and practical experience gained from this workshop are expected to further strengthen officers' skills in producing high-quality pharmacovigilance articles, thus enhancing effective communication of safety information to healthcare professionals.

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Denosumab and Biosimilars	Multi Vertebral Fractures (MVF) after Discontinuation of Denosumab – Strengthened Warnings	19-Mar-2026	-
2	Mycophenolate mofetil	Anaphylactic Reaction [DHPC]	19-Mar-2026	-

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit www.npra.gov.my
2. Report ADR as Healthcare Professional

   Download the ADR manual form and submit the completed form via email or post:

   fv@npra.gov.my

   Pharmacovigilance Section,
   National Pharmaceutical Regulatory Agency (NPRA),
   Ministry of Health, Malaysia.
   Lot 36, Jalan Prof Diraja Ungku Aziz (Jalan Universiti),
   46200 Petaling Jaya, Selangor, Malaysia.

NPRA Safety Information Mailing List

To join the mailing list:

a) scan the QR code to complete the subscription form, or

b) send an email with your details to fv@npra.gov.my