THIS FINDING IS SUBJECT TO PROHIBITIONS AND RESTRICTIONS ON PUBLICATION UNDER S 74 OF THE CORONERS ACT 2006

IN THE CORONERS COURT **CSU 2021-AUK-001059**
AT AUCKLAND
(IN CHAMBERS)

I TE KŌTI KAITIROTIRO MATEWHAWHATI
KI TĀMAKI MAKAURAU
(I TE TARI)

UNDER **THE CORONERS ACT 2006**

AND

IN THE MATTER OF **An inquiry into the death of ISABELLA RANGIMOHIA ALEXANDER**

Date of Findings: 7 December 2022

FINDINGS OF CORONER J ANDERSON

Introduction

[1] Isabella Rangimohia Alexander, aged 17, collapsed while out walking at Muriwai Beach with her father on 9 September 2021. She became short of breath and fell over, unable to breathe. Isabella's father, Michael, ran the short distance to their home to get his telephone and alert Isabella's mother. As they returned to assist Isabella, Michael contacted emergency services and called a nearby friend who had a defibrillator. They commenced CPR and attempted to revive Isabella while waiting for paramedics to arrive.

[2] Isabella was transferred by helicopter to Auckland City Hospital. Upon arrival, she was deeply unconscious. Isabella was found to have significant bilateral pulmonary emboli (clots in the blood vessels of her lungs) and medical staff suspected that she had experienced an irreversible global hypoxic brain injury.

[3] Isabella's condition deteriorated during the night and, due to her condition, it was determined that no resuscitation attempts would be made if she went into cardiac arrest. At 5:40am on 10 September 2021 Isabella's heart stopped beating and she was confirmed to have passed away.

[4] Following Isabella's death, her parents raised concerns about the medical care that she received prior to her admission to hospital. It was also noted that Isabella had been taking the contraceptive pill and had recently received the Pfizer Covid-19 vaccine. As a result of these matters, her death was referred to the national duty coroner. The national duty coroner considered that Isabella's death was a reportable death that came within the provisions of s 14 of the Coroners Act 2006 ("the Act") and accepted jurisdiction. Responsibility for matters relating to Isabella's death was subsequently transferred to me and I opened a coronial inquiry into the circumstances of Isabella's death, in accordance with s 59 of the Act.

Purpose of this inquiry

[5] Section 57 of the Act requires a coroner to conduct an inquiry, not to determine civil, criminal or disciplinary liability but to establish, so far as is possible, that a person has died, the person's identity, when and where the person died, the causes of the death and the circumstances of the death.

[6] A coroner can also make recommendations and comments in relation to a death which may, if drawn to public attention, reduce the chances of further deaths occurring in similar circumstances.[1]

Is an inquest hearing required?

[7] I have reviewed the evidence obtained during the course of the inquiry into Isabella's death. This includes witness statements and other information provided by the police, reports from relevant medical professionals and expert opinions provided by an independent general practitioner adviser and a specialist haematologist who is also an obstetric physician.

[1] Coroners Act 2006, ss 57(3) and 57A

[8] I have considered whether it is necessary or desirable to hold an inquest hearing into Isabella's death. I have formed the view that I can determine the matters that I am required to decide based on the evidence already available to me and that an inquest hearing is not required.

[9] Having given notice to relevant parties, I have decided to conclude this inquiry by issuing written findings in accordance with s 77 of the Act.

Summary of findings

[10] I have formed the view that Isabella died of pulmonary thromboembolism. After her death, Isabella was found to have a rare blood mutation (heterozygous Factor V Leiden mutation). This condition, in combination with the use of the combined oral contraceptive pill, contributed to the development of the pulmonary thromboembolism. There is no evidence available to me to suggest that the Pfizer vaccine had any role in her death.

[11] Isabella's tragic death is a reminder of the dangers posed by medications that are generally regarded as safe and effective. Due to her underlying genetic disorder, Isabella was at increased risk of pulmonary embolism, which is a rare but well documented risk of taking hormonal contraceptive medication. While Isabella did not know that she had this disorder, and was therefore at increased risk of a thromboembolism, this condition can occur even in the absence of a Factor V Leiden mutation.

[12] It is particularly important for people who take hormonal contraceptives, and other hormone-based medications, to know the warning signs and symptoms of thromboembolism and to have a low threshold for seeking medical advice. It is also essential for health providers to be vigilant for the risks and signs, which can be hard to identify. For these reasons, I have made a number of recommendations pursuant to s 57 of the Act, for the purposes of reducing the chances of similar deaths occurring in future. These recommendations are set out at the end of my findings.

Cause of death

[13] Following Isabella's death consideration was given to whether a post mortem examination was required. Through the extensive diagnostic testing already carried out by the Auckland City Hospital doctors, the immediate cause of Isabella's death was known

to be a pulmonary embolism. In consultation with the duty pathologist, the duty coroner determined that a lesser post mortem was required, rather than a full post mortem. It was decided that this would be performed in conjunction with additional testing of blood samples that were obtained prior to Isabella's death. A lesser post mortem consists of an external examination, a CT scan, examination of relevant medical records and toxicology testing of blood samples. The duty pathologist was of the view that a full post mortem, including an internal examination, would not provide any additional useful information in the circumstances.

[14] The lesser post mortem examination was performed by forensic pathologist Dr Tse. He advised me that the examination did not reveal any findings that were not already appreciated during Isabella's hospital treatment. However, molecular hematologic testing on blood collected during her hospital stay showed heterozygous Factor V Leiden mutation. This condition can increase the risk of thrombosis and is discussed in more detail later in these findings. It is an inherited genetic abnormality associated with an increased risk of venous blood clots. Dr Tse advised that the direct cause of Isabella's death was pulmonary thromboembolism. Antecedent causes were heterozygous factor V Leiden mutation, exacerbated by recent commencement of the contraceptive pill. I accept Dr Tse's advice regarding the cause of Isabella's death.

Family concerns

[15] Isabella's family has provided information about her background for the purposes of this inquiry. Isabella's mother, Teresa, advised that Isabella was very bright and had received fast track acceptance into Auckland University Law School for 2022. She was also asked to join a high achiever mentoring programme. Isabella had previously been a competitive national level swimmer and trained regularly. Her parents advised that she was less fit in the years immediately prior to her death, although she still played netball several times a week.

[16] Like many teenagers, Isabella liked to socialise and attend parties. She had also started vaping, unbeknown to her mother. During 2021 Teresa found out that Isabella was taking the contraceptive pill. She had been accessing this via a friend, who had been obtaining it from her own school nurse, stating it was for her personal use. She was then

passing the medication on to Isabella. Isabella attended a religious school so was not able to access the medication directly through her own school nurse.

[17] On 22 June 2021 Isabella was admitted overnight to hospital. She was referred by her GP with a sore throat, migratory arthralgia (sore joints) and a newly noted heart murmur. There were concerns that she had rheumatic fever. At the time, several members of Isabella's family were ill with viral upper respiratory tract infections. Isabella described an ongoing cough and an itchy red rash on her anterior thighs and abdomen that resolved within several days. She said she normally got a rash like that when she was unwell, and she did not describe any angioedema (swelling underneath the skin). The clinical notes from the admission record that Isabella stated that she had occasional joint pains in her ankles and knees related to netball and other sports but had no history of migratory inflammatory polyarthralgia (pain in multiple joints). Based on the information Isabella provided, it was recorded that she was not taking any medications and had never smoked.

[18] Isabella was noted to be alert and well and did not have a raised temperature during her hospital stay. No murmur was detected on testing, but it was noted that one had been heard on her admission to hospital. Her chest was clear. An ECG was performed, and this identified a normal sinus rhythm. There was no evidence of a prolonged PR interval, which might have indicated that there were problems with the electrical conduction within her heart. Her chest X-ray was also clear and a full blood count, peripheral blood cultures, respiratory panel PCR tests, C reactive protein test, serum/plasma testing, serology and urine tests were all normal. The clinical impression was that Isabella had a viral upper respiratory tract infection with related viral rash, rather than rheumatic fever.

[19] Isabella was discharged home with instructions regarding symptomatic relief for her cough. Due to delays in arranging an inpatient echocardiogram, and a long wait for a community one, it was decided that a private echocardiogram would be arranged by her parents after discharge. The purpose was to check for any signs of carditis or valve disease. This was performed on 29 July 2021 and the results are reported to have been normal.

[20] On 9 July 2021 Teresa took Isabella to an appointment at a medical clinic in Ponsonby. Isabella had not previously been seen at the clinic and she attended as a casual patient. She did not want Teresa to go in with her. Isabella was seen by a locum doctor at the practice. She did not state who her usual GP was when she completed the registration

form and health questionnaire. She did not disclose any history of blood clots or Factor V Leiden mutation, and answered "no" to all other routine risk assessment questions. She told the doctor that she had been taking the combined contraceptive pill Levlen for 4 months, without any issues. She said she had been obtaining this from a friend. She did record that she had a heart murmur that was going to be investigated further in several weeks' time.

[21] The doctor proceeded to prescribe Levlen ED (1 tablet daily), and this was dispensed by a nearby pharmacy later the same day. Levlen ED is a combined oral contraceptive pill that contains the active ingredients ethinylestradiol and levonorgesterel. The standard medication information[2] states that you should not take Levlen ED if you have, or have had, any blood clotting disorders such as Factor V Leiden mutation, or if you are at high risk of blood clots or have a number of other medical conditions. Isabella, of course, was not aware that she had Factor V Leiden mutation at the time she commenced taking this medication.

[22] The information sheet also contains information about the symptoms of an allergic reaction to Levlen ED, including shortness of breath, wheezing or difficulty breathing, swelling of the face and a rash, itch or hives on the skin, as well as the following information:

> ***Do not take Levlen ED if you have or have had a blood clot in:***
>
> • *the blood vessels of the legs (deep vein thrombosis - DVT)*
>
> • *the lungs (pulmonary embolism - PE)*
>
> • *the heart (heart attack)*
>
> • *the brain (stroke)*
>
> • *other parts of the body.*

[2] https://www.medsafe.govt.nz/consumers/cmi/l/levlen.pdf

Do not take Levlen ED if you have or are concerned about an increased risk of blood clots

Blood clots are rare. Very occasionally blood clots may cause serious permanent disability, and may even be fatal. You are more at risk of having a blood clot when you take the Pill. However, the risk of having a blood clot when taking the Pill is less than the risk of having a blood clot during pregnancy.

Blood clots and the Pill

Blood clots may block blood vessels in your body. This type of blood clot is also called thrombosis.

Blood clots sometimes occur in the deep veins of the legs. If a blood clot breaks away from the veins where it has formed, it may reach and block the blood vessels of the lungs, causing pulmonary embolism.

Blood clots can also occur in the blood vessels of the heart (causing a heart attack) or the brain (causing a stroke). Blood clots are a rare occurrence and can develop whether or not you are taking the Pill. They can also happen during pregnancy. The risk of having blood clots is higher in Pill users than in non-users, but not as high as during pregnancy.

The risk of a blood clot is highest during the first year of taking the Pill for the first time, or after having a break from the Pill for 4 weeks or more.

If you notice possible signs of a blood clot, stop taking Levlen ED and consult your doctor immediately. *To prevent pregnancy, you must also use additional barrier contraceptive precautions (e.g. condoms or a diaphragm). If you are concerned about an increased risk of blood clots while on Levlen ED, speak to your doctor.*

[23] On 26 August 2021 Isabella received her first dose of the Pfizer BioNTech Covid-19 vaccine. Her mother reported that nothing major seemed to change after this, but that Isabella still complained of being breathless and her face looked a bit puffy. In early September, Teresa became concerned when Isabella told her that she had not had a period for three months. She told her mother that she was taking the contraceptive tablets continuously, rather than taking the active tablets for three weeks every month and then the placebo sugar tablets for the last week of each cycle. Isabella said "all the girls were doing it" to avoid having a period. Teresa was concerned that Isabella's symptoms could be related to this practice and she arranged a medical appointment.

[24] Isabella subsequently had a telephone consultation with Dr He. This took place on 6 September 2021, during the Auckland level 4 Covid-19 lockdown. Isabella reported a five-day history of night time and exercise induced wheeze. This started in the morning when waking up in her bedroom, after she had left the caps off her acrylic paints overnight. She had started painting as a new hobby during the lockdown and thought that the paint fumes might be making her wheezy. Isabella reported that she had been sleeping well and denied any chest pain. However, she said she had hot and cold flushes and a bit of light headedness. She was eating and drinking normally and said she had been out for several runs over the previous days, but this had brought on a wheeze. She sounded comfortable when talking and was speaking in full sentences over the telephone.

[25] Dr He asked Isabella to come into the surgery for an assessment. He saw Isabella and Teresa in a dedicated viral room separate from the GP practice, wearing full PPE. He advised me that Isabella looked well, with no signs of distress, when she walked from the car to the room. On examining her, he found that her vital observations were stable. Her temperature was 36.2°C and the pulse oximeter revealed that her heart rate was 90bpm, with an oxygen saturation of 98%. He checked her pulse which was regular in rhythm and her chest was clear when auscultated, with normal breathing throughout all areas. Her ears and throat appeared normal when examined and there were no features of facial oedema. His diagnosis was of bronchospasm caused by inhalation of acrylic paint. He discussed this with Isabella and Teresa, including the option of using an inhaler. Although he had not heard any wheezing, he thought a short acting beta antagonist might reduce a bronchospasm induced wheeze. However, Isabella indicated that the wheeze was getting better and that she preferred not to use an inhaler. Dr He reported that he gave "safety netting" advice to come back if she got any worse, had a fever or didn't improve.

[26] Dr He advised that during the consultation, there was some discussion about increasing Isabella's level of activity. This had reduced during the Covid lockdowns, with Isabella spending a lot of time in her room and using electronic devices. He suggested that regular daily activity was healthy, but to wait for Isabella's wheeze to subside first.

[27] During the appointment, Isabella asked Dr He whether it was wrong to take Levlen continually, as she had been doing. She said her mum wanted her to follow the instructions on the pill packet, taking a week of placebo (sugar) pills each month and having a period at the end of each cycle. Dr He said that he explained that either option was "ok". Teresa

recalled speaking to Dr He about the possibility that Isabella's symptoms could be an allergic reaction to the contraceptive pill, and that she showed him some of the symptoms on her phone. Dr He advised that he does not recall this particular aspect of the discussion, but he did go through the symptoms that might represent a severe allergic reaction, such as facial, lip and tongue swelling. He did not find these present when he assessed Isabella.

Police inquiries

[28] Police carried out a thorough investigation after Isabella passed away and interviewed relevant witnesses. Investigating police have advised, via the inquest officer, that they are satisfied that there is nothing suspicious or untoward in relation to Isabella's death. No evidence was found to indicate the involvement of any other person in the death. I accept this advice.

Concerns raised by Isabella's uncle

[29] During the course of the inquiry Into Isabella's death, I received information from her paternal uncle. He raised a number of concerns about the potential role of the Pfizer vaccine in Isabella's death. He indicated that he "had seen evidence out of Israel and the USA of the Pfizer vaccine causing various side effects including blood clotting", and he wanted an investigation into whether the vaccine may have been a primary or contributing cause.

[30] I note that in the early stages of the inquiry into Isabella's death, I sought information from the Covid-19 Vaccine Independent Safety Monitoring Board and CARM, the Centre for Adverse Reactions Monitoring. The Board confirmed that on the basis of the available information, the pulmonary embolism that Isabella experienced was unlikely to be related to the administration of the Pfizer vaccine.

Expert medical advice

[31] For the purposes of my inquiry into Isabella's death, I obtained independent expert medical advice from a specialist general practitioner adviser and a specialist haematologist/obstetric physician. I asked the general practice adviser to comment on aspects of the medical treatment that Isabella received prior to her death. I requested expert advice from the specialist haematologist/obstetrician about the nature of Factor V Leiden

mutation, the relationship between this mutation and thromboembolism, and information about any increased risks associated with either the oral contraceptive pill or the Pfizer vaccine.

Independent General Practitioner Advice

[32] Dr Murdoch, the general practice adviser, informed me that the locum GP who saw Isabella in July 2021 had ascertained that Isabella was not a smoker, and had no personal history of migraine or family history of venous thromboembolism or breast cancer. She was not overweight, had a normal blood pressure (120/80) and had already been using the pill for four months with no problems. Dr Murdoch considered that the care provided by the locum GP was entirely consistent with good practice. She advised that there was no reason to test for Factor V Leiden mutation at the time, particularly given that Isabella reported no family history of venous thromboembolism.

[33] In relation to the consultation with Dr He on 6 September, Dr Murdoch noted that the care that he provided was entirely consistent with good practice. There were no indications pointing to a diagnosis of pulmonary thromboembolism. She noted that Isabella reported a five-day history of wheeziness, worse at night time and when exercising but not present at rest. She had no chest pain but did feel a bit light headed. The symptoms coincided with exposure to acrylic paint fumes in her bedroom. She had no history of asthma. On examination, she was not breathless and did not have a fever. Her pulse was mildly elevated at 90 beats per minute, and her oxygen levels were normal at 98%. Her throat looked normal and there was no swelling in her face, lips or tongue. Her lungs were clear on auscultation. Dr He felt the likely diagnosis was bronchospasm caused by acrylic paint fumes. Isabella reported that the paint had been removed from her bedroom and her symptoms were improving. Dr He offered an inhaler to help ease the wheeze, but Isabella opted to wait and see if her symptoms continued to improve.

Expert haematologist/obstetric advice

[34] Dr McLintock is a highly respected specialist haematologist and obstetric physician. She is the President of the International Society on Thrombosis and Haemostasis and is a past president of the Society of Obstetric Medicine of Australia and New Zealand. She is also a Council Member of the Asia Pacific Society of Thrombosis and Haemostasis.

[35] I have reproduced the content of Dr McLintock's advice at considerable length. Dr McLintock has provided very relevant and useful information relating to the matters that I have considered for the purposes of this inquiry. I have included the specific questions that I asked her, and her responses:

> ***Can you please provide an explanation of Factor V Leiden mutation, including the nature of the mutation, its prevalence and the impact on individuals who have the mutation?***
>
> *Blood clotting and bleeding is a tightly controlled physiological process, with a complex set of checks and balances to ensure that pathological activation of either process does not occur. A blood clot normally forms to stop bleeding after surgery or injury with the blood clot or "thrombus" forming at the site of injury. Blood clots can also form as a result of pathological increases in clotting factors or changes in blood flow or inflammation. When the blood clotting system is activated, the system to breakdown clots is activated at the same time to ensure that the development of the blood clot is controlled. Factor V is one of the clotting proteins important in the augmentation of blood clotting but also important in the switch off mechanism, for stimulation of blood clots. Under normal circumstances, Factor V becomes activated and dampens down the signals that promote blood clotting. Factor V Leiden (FVL) is a mutation in clotting factor V that makes it more resistant to activation, and therefore not as effective at switching off the stimulus to clotting, and makes a person's blood more "sticky" or more likely to from clots or thrombosis. This is why it is known as a "thrombophilia" – a clotting tendency.*[3]
>
> *FVL is an inherited genetic abnormality, thought to have occurred about 20 000 years ago, and is associated with an increased risk of forming venous blood clots, i.e. venous thromboembolism (VTE). These present clinically as a deep vein thrombosis (blood clot in the deep veins of the leg) and/or a pulmonary embolism (a blood clot in the arteries in the lung). The majority of people inherit only one abnormal copy of the mutation and are described as being heterozygous for mutation, but a smaller number of people have two abnormal copies and are described as being homozygous. The inheritance pattern is autosomal dominant, so a person has a 50/50 chance of inheriting it from an affected parent. The heterozygous state (i.e. only one abnormal gene copy) is described in approximately 5% of people of Caucasian ethnicity and is rarely described in people of other ethnicities. FV Leiden was first reported in the 1990s by clinical and laboratory researchers in the city of Leiden in the Netherlands.*[4]
>
> *Although FVL is one of the most common genetic risk factors for VTE it is not a very strong thrombophilia and does not make the blood very clotty. Being heterozygous for FVL increases*

[3] Van Cott et al. *Factor V Leiden*. Am J Hematol. Vol. 91, No. 1, January 2016 doi:10.1002/ajh.24222
[4] Dahlback B, Carlsson M, Svensson PJ. *Familialthrombophilia due to a previously unrecognizedmechanism characterized by poor anticoagulantresponse to activated protein C: Prediction of acofactor to activated protein C*. Proc Natl AcadSci USA 1993; 90:1004–1008

the risk of developing venous thromboembolism (VTE) by a factor of about 5-10 times the background risk. However, it is not inevitable that everyone who is heterozygous for FVL will develop a blood clot, with this reported in fewer than 50% of people heterozygous for FVL. Most commonly the VTE will occur in individuals with FVL who have additional risk factors for thrombosis or blood clots such as surgery, hospital admission with severe illness, pregnancy, cancer and oestrogen containing hormonal contraceptive pills.

How is Factor V Leiden mutation identified? How is the testing performed and what are the indications for testing?

Factor V Leiden is identified by a blood test that screens for the presence of "sticky" blood and then, if the screening test is positive, the mutation can be specifically identified using a laboratory test confirming the presence of the genetic mutation. When the mutation was first discovered in the 1990s it was hypothesised that the presence of the mutation could be used to screen for people who had a history of VTE and identify those in whom more targeted anticoagulation therapy would be required. It was thought that the presence of FVL could help identify those at highest risk of recurrent VTE and therefore direct treatment with anticoagulation. However, that early optimism has not been realised and, while FVL is a risk factor for development of the first VTE, it is not helpful in identifying people at risk of recurrent VTE. Also not everyone with FVL will inevitably develop VTE; fewer that 50% will, so routine screening prior to risk events such as starting COC or have major surgery has not shown clinical benefit for risk prediction.

Current international practice recommendations do not routinely recommend testing people with VTE for the mutation as finding it does not help identify those at higher risk of recurrent clots and is not a useful tool in decisions regarding anticoagulation choices in this group of patients.[5] [6]

Would there be any benefit in routinely testing individuals for the presence of this mutation?

See above.

Would there be any benefit in testing for this mutation prior to commencement of the contraceptive pill?

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[5] van Vlijmen EFW, Wiewel-Verschueren S, Monster TBM, Meijer K. *Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis.* J Thromb Haemost 2016; 14: 1393–403

[6] Faculty of Sexual & Reproductive Healthcare (FSRH). *Combined Hormonal Contraception (January 2019, amended November 2020).* Accessed https://www.fsrh.org/standards-and-guidance/documents/combined-hormonal-contraception/

To answer this question one must take into consideration how such universal screening would affect individuals found to have the mutation and those who do not have the mutation and how it would impact their clinical outcome. Would finding the mutation inform the patient and clinician about a significant risk of thrombosis that otherwise would be unknown?

The combined oral contraceptive pill (COC) contains oestrogen and progesterone and is a known risk factor for developing venous thromboembolism (VTE), associated with a 2-15 fold increased risk of VTE depending on the type hormones in the COC pill.

The earlier forms of COC, second generation pills, carry the lowest risk of VTE, increasing the risk 2-3 fold. Third generation pills increase the risk 3-5 fold, and some of the newest ones that are used for treating conditions such as acne increase the VTE risk up to 15 times. These increases in relative risk of VTE should be seen in the context of the background risk of VTE in women of childbearing age which is around 1-2 in 10,000.[7]

Data compiled by the World Health Organization (WHO) for developed countries in 1997 suggests that the VTE event rate, among non-pregnant women who are not using COCs, increases with age:

1. Age	***2. VTE event rate***
3. 20 to 24 years	*4. 3.2 events per 100,000 woman-years*
5. 30 to 34 years	*6. 4.6 events per 100,000 woman-years*
7. 40 to 44 years	*8. 5.9 events per 100,000 woman-years*

In association with COC use, the risk of VTE is considered to be highest in the first year of use. VTE risk also rises with increasing oestrogen dose and depends on the type of progesterone.

Epidemiological studies suggest the incidence of VTE in women, with no known risk factors, who use low oestrogen dose COCs (<50 µg) ranges from 20 to 40 cases per 100,000 woman-years. This rate equates to a four to eight-fold increased risk of VTE compared with non-pregnant nonusers for whom an estimated event rate range is 5 to 10 cases per 100,000 woman-years.[8]

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[7] van Vlijmen EFW, Wiewel-Verschueren S, Monster TBM, Meijer K. *Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis.* J Thromb Haemost 2016; 14: 1393–403

[8] *Combined oral contraceptives and VTE - putting the risk into perspective.* https://www.medsafe.govt.nz/profs/puarticles/CombinedOralContraceptives

Of the small number of VTE events that do occur during use of COC, approximately 1% are fatal and this can happen in otherwise fit and healthy individuals.[9]

In conjunction with heterozygosity for Factor V Leiden, among combined oral contraceptive users the risk of VTE increases the risk of venous thrombosis six-fold (odds ratio 5.9, 95% CI – 8.2). A Swedish case control study showed that the use of combined oral contraceptive pills was associated with a 3.4 increased VTE risk and that Factor V Leiden had a 2.6-fold increased risk of VTE but in combination the risk of VTE was increased to 20.6-fold.[10]

However, the risk of VTE is also influenced by other factors in addition to hormonal exposure such as the woman's age, family history of VTE, and lifestyle factors such as weight and smoking.

Finding FVL in the absence of a family history of VTE cannot be linked to its relevance with regards clinical outcome. In an individual who has no family history, the relevance is less certain.

Given that the prevalence of FVL in the Caucasian population is 5%, screening of the general population for FVL would identify 1 in 20 women as having the mutation. If these women were not offered the COC on the basis of this result alone, [they] would be denied this very effective and generally well-tolerated form of birth control……. This could result in a less effective contraceptive being offered which may lead to an unplanned pregnancy, which carries a much higher risk of venous thromboembolism than the combined oral contraceptive pill.

Can a negative thrombophilia test be helpful? A negative thrombophilia screen does not identify women who are not at increased risk of developing VTE and may falsely reassure some people.

Despite early hopes that screening for Factor V Leiden could be an important tool in risk stratification for VTE, research published since its discovery has not confirmed that it plays a critical role. Current international recommendations do not recommend routine testing for these clotting tendencies in people who have had a VTE or who might be facing a situation associated with increased clotting risks, as the finding of a thrombophilia such as FVL has not been shown to be of clinical benefit.

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[9] Hedenmalm K, Samuelsson E. *Fatal venous thromboembolism associated with different combined oral contraceptives: a study of incidences and potential biases in spontaneous reporting.* Drug Safety(?) 2005;28:907–16.

[10] Blondon M. Understanding and Management of Venous Thromboembolism (VTE) – Section 17. Update On Oral Contraception And Venous Thromboembolism. https://ehaweb.org/assets/Uploads/Congresses/EHA25/Education-Book-Pre-release/HemaSphere-2020-0015.pdf

In the last decade the recommendations for testing for thrombophilias have become narrower and narrower. One situation where testing may be recommended is in the presence of a family history of VTE when a thrombophilia such as FVL has been identified in the index case in the family (i.e the person who first developed a thrombosis). However, as most authorities now do not recommend testing the majority of people with VTE for inherited thrombophilias, such examples are less and less commonly found.

The Royal College of Obstetricians and Gynaecologists in the United Kingdom and the Centres for Disease Control and Prevention in the USA do not recommend routine thrombophilia screening before prescribing the combined hormonal oral contraceptive pill.[11] [12] *The Royal Australian and New Zealand College of Obstetricians and Gynaecologists endorse the advice from the UK in their guidelines re prescription of the combined hormonal oral contraceptive pill.*[13]

There is no benefit overall to recommend screening for inherited thrombophilia i.e. clotting tendencies prior to starting the combined oral contraceptive pill or exposure to other risk events such as surgery and pregnancy.

Are you aware of any information suggesting that there is an increased risk of mortality or morbidity for individuals with Factor V Leiden mutation who take the contraceptive pill?

I am not aware of data to support increased mortality in individuals who have FVL who take the contraceptive pill. These individuals do have an increased risk of VTE as outlined above but this is not associated with an increased risk of death from VTE or other causes.

Are you aware of any information suggesting that there is an increased risk of mortality or morbidity for individuals with Factor V Leiden mutation who receive the Pfizer Covid-19 vaccine?

There are no data to suggest that people with FVL who have received the Pfizer Covid-19 vaccine are at increased risk of morbidity and mortality. Importantly there is no evidence that people who have received Pfizer Covid-19 vaccine are at an increased risk of venous

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[11] Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, et al. *Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.* Health Technol Assess 2006;10 (11).

[12] *Faculty of Sexual & Reproductive Healthcare (FSRH). Combined Hormonal Contraception (January 2019, amended November 2020).* Accessed https://www.fsrh.org/standards-and-guidance/documents/combined-hormonal-contraception/

[13] *Combined Oral Contraceptive.* Royal Australian and New Zealand College of Obstetricians and Gynaecologists RANZCOG https://ranzcog.edu.au/wp-content/uploads/2022/05/Combined-hormonal-contraceptives.pdf

thromboembolism. While an epidemiological study[14] *showed an increased risk of thrombotic episodes and thrombocytopenia in adults under 65 years of age within one month of the AstraZeneca ChAdOx1 vaccine, the BNT162b2 vaccine (mRNA Pfizer Covid vaccine) was not associated with an increased risk of thrombosis.*

Are you aware of any information that would suggest that vaping increases the risk of thromboembolism, either for those with or without Leiden Factor V mutation?

Recent studies are showing emerging data of an association between vaping and development of VTE possibly due to activation of clotting cells called platelets or direct damage to lung blood vessels. [15] [16] *Data from large cohort studies is not yet available.*

Are you aware of any information that would suggest that continued use of the active contraceptive pill tablets (rather than taking active and sugar tablets as per packet direction) increases the risk of thromboembolism either for those with or without Leiden Factor V mutation?

Continuous cycle COC, continuing the active oestrogen/progesterone tablets for 3-6 months or more, omitting the 7 days of sugar pills, are being increasingly used. This approach means that users can avoid having a monthly withdrawal bleed. Many users find this more convenient, and it has the potential to provide more secure contraception. A systematic review of outcomes with this approach compared to the standard 21-day pill with a 7-day break does not show an increase in the risk of serious adverse events with continuous cycle COC due to the extended exposure to oestrogen in extended COC and oestrogen-supplemented regimens.[17]

Data is reassuring not only of the safety of continuous cycle COC but also that it is an effective, well-tolerated and often preferred method of contraception.[18]

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[14] *Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and the BNT162b2 Covid-19 vaccines: A national cohort study in England. Andrews et al.* Lancet 2022; Vol 13; February.
https://www.sciencedirect.com/science/article/pii/S2666776221002465?via%3Dihub

[15] Ramirez JEM et al. *The JUUL E-Cigarette Elevates the Risk of Thrombosis and Potentiates Platelet Activation.* J Cardiovasc Pharmacol Ther. 2020 Nov;25(6):578-586 doi:10.1177/1074248420941681. Epub 2020 Jul 21

[16] Light PM et al. *Unprovoked Pulmonary Embolism Despite Prophylaxis as a Sequela of E-cigarette or Vape-Associated Lung Injury (EVALI).* Am J Resp Crit Care Med 2020;201:A6681

[17] Edelman A, Micks E, Gallo MF, et al. *Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception.* Cochrane Database Syst Rev 2014;CD004695

[18] Nappi et al. BMC Women's Health (2018) 18:22. *Real-world experience of women using extended-cycle vs monthly-cycle combined oral contraception in the United States: the National Health and Wellness Survey*

Are there any other matters or comments that would be of assistance?

The UK Faculty of Sexual and Reproductive Healthcare provide very useful information about all aspects to consider when considering the COC for patients. They recommend that specific attention should be given to enquiring about the following prior to prescribing COC:[19]

- *Thrombophilia or previous VTE*
- *Ischaemic heart disease, stroke or transient ischaemic attack, peripheral vascular disease*
- *Additional risk factors for venous or arterial thromboembolism (e.g. smoking, obesity, recent childbirth, immobility, hypertension, migraine, diabetes, hyperlipidaemia, antiphospholipid antibodies, arrhythmia, complicated congenital/valvular heart disease or cardiomyopathy)*
- *Personal history of breast cancer/known breast cancer-related gene mutation*
- *Hepatobiliary disease*
- *Recent childbirth, current breastfeeding.*

While some guidelines recommended against use of COC in women with known thrombophilias, a recent systemic review and meta-analysis concludes that the VTE risk of mild thrombophilia such as FVL heterozygosity is modest and that when no other risk factors are present, (e.g. family history) COCs can be offered to these women when reliable alternative contraceptives are not tolerated.[20]

[36] Dr McLintock noted that there was no documentary evidence that the GP who prescribed the contraceptive pill to Isabella discussed the potential risks of the combined oral contraceptive pill with her. She also noted that Dr He did not consider a diagnosis of VTE as a differential diagnosis for Isabella's symptoms during the appointment on 6 September 2021. She indicated that a blood test called a D-dimer could have been taken at this time to either exclude thrombosis or prompt further investigation. Dr McLintock advised that if Isabella's respiratory rate had been recorded at the consultation, and this

[19] Faculty of Sexual & Reproductive Healthcare (FSRH*). Combined Hormonal Contraception* (January 2019, amended November 2020).

[20] *van Vlijmen EFW, Wiewel-Verschueren S, Monster TBM, Meijer K. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2016; 14: 1393–403.*

had been abnormal, this could have helped point to the need for further investigation. She considered that there had been a missed opportunity to investigate Isabella's new onset respiratory symptoms, and that this could potentially have led to the pulmonary embolism being diagnosed and treated earlier.

[37] Dr McLintock concluded as follows:

> ***Conclusion***
>
> *In conclusion, both the combined oral contraceptive pill and her undiagnosed heterozygosity for the Factor V Leiden mutation would have contributed to the development of Isabella's fatal pulmonary embolism. In addition, Isabella's GP missed an opportunity to investigate further for thrombosis when he saw her on 6 September 2021 when he failed to consider pulmonary embolism as an explanation for her new onset respiratory symptoms. Dr He did not record Isabella's respiratory rate at this in-person consultation, and this should be done in all patients with respiratory symptoms as it is often one of the first signs of significant respiratory compromise in an otherwise healthy young person.*
>
> *Although the risk of VTE is increased in users of combined hormonal oral contraceptives, with and without Factor V Leiden, the absolute risk of VTE is very small. Isabella's risk was increased from a background risk of 1 in 10000 for someone of her age, to 20 in 10 000 (1 in 500). She had no additional risk factors for venous thromboembolism (VTE) that would be a contraindication to prescription of the combined hormonal oral contraceptive pill. She was not overweight, was not a regular smoker and had no family history of VTE.*
>
> *Taking the combined oral contraceptive pill in a continuous fashion has not been shown to increase the risk of VTE. International recommendations do not support screening of the general population for thrombophilias prior to risk events including initiation of combined oral contraceptive pill.*
>
> *There is no evidence to suggest that the Pfizer Covid-19 mRNA vaccine is associated with an increased risk in development of VTE so this is not likely to have contributed to development of the fatal pulmonary embolism.*
>
> *Doctors should take a complete history prior to prescribing the combined oral contraceptive pill to women to ensure they have no additional risk factors for VTE.*

> *Importantly, the signs and symptoms of VTE should be discussed with each woman so that she can present promptly for assessment if she develops signs or symptoms of concern.*
>
> *Testing for inherited clotting tendencies in the absence of a family history or personal history of VTE is not recommended as its clinical utility is uncertain and universal screening would lead to some women being denied this form of contraceptive birth control.*
>
> *There was a missed opportunity to investigate Isabella's new onset respiratory symptoms when she presented to her GP on September 6th which could potentially have led to the pulmonary embolism being diagnosed and treated earlier. In particular, recording the respiratory rate at that consultation could have helped point to the need for further investigation if it had been abnormal.*

Further advice from Dr Murdoch

[38] After receiving the advice from Dr McLintock, I asked Dr Murdoch to consider her earlier advice to me, in light of Dr McLintock's comments regarding the potential missed opportunity to investigate Isabella's symptoms further following the consultation with Dr He on 6 September 2021.

[39] Dr Murdoch advised that when Dr He saw Isabella, he recorded that she was not breathless. Dr Murdoch regarded this documented observation as a satisfactory alternative to measuring and documenting her respiratory rate. She agreed that Dr He did not appear to consider a pulmonary thromboembolism as a possible diagnosis and therefore did not arrange a D-dimer blood test. Dr Murdoch believed this was acceptable. She noted that pulmonary thromboembolism can be very difficult to diagnose as it can present with very few clinical symptoms or signs. She confirmed the view expressed in her original report to me, that there were no indications pointing to this diagnosis on 6 September 2021.

Findings

[40] I find that Isabella Rangiamohia Alexander died at Auckland Hospital on 10 September 2021 of pulmonary thromboembolism, caused by heterozygous Factor V Leiden mutation, exacerbated by recent commencement of the oral contraceptive pill.

[41] For the sake of completeness, I note the concerns raised by Isabella's uncle about the possible association between the Pfizer vaccine and Isabella's death. There is no evidence available to me to suggest that the vaccine played any role in causing Isabella's death. In contrast, there is compelling independent medical evidence that her death from pulmonary thromboembolism was caused by a combination of an underlying genetic condition Factor V Leiden mutation, and the recent commencement of the oral contraceptive pill.

Recommendations / Comments

[42] Isabella's death is a reminder that widely used, and relatively safe, medications still have risks. These can include rare and serious side effects, and even death. It is important to be alert to these risks and the associated warning signs. Even healthy young people, who appear to have no obvious risk factors, can be affected. Those who have known risk factors need to be particularly vigilant.

[43] While there is nothing that can be done to bring Isabella back, her tragic death highlights some important public health issues. In order to help reduce the chance of similar deaths occurring in future, I make the following recommendations under s 57B of the Act:

(a) All prescribers of the combined oral contraceptive pill, and other hormone related medications, should ensure that they take a comprehensive clinical history and must inform patients about the risks of venous thromboembolism (VTE), the seriousness of the condition, and the symptoms to look out for. In relation to deep vein thrombosis (DVT) these symptoms include:[21]

- Leg pain or tenderness in the thigh or calf
- Leg swelling (oedema)
- Skin that feels warm to the touch
- Reddish discolouration and streaks

[21] https://www.heart.org/en/health-topics/venous-thromboembolism/symptoms-and-diagnosis-of-venous-thromboembolism-vte

(b) Patients should also be advised that when a DVT breaks free from a vein wall and blocks some of the blood supply to the lungs, this can cause a pulmonary embolism which can be fatal. The symptoms include:

- Unexplained shortness of breath
- Rapid breathing
- Chest pain anywhere under the rib cage
- Fast heart rate
- Light headedness and passing out.

(c) People who take the combined oral contraceptive pill, or other hormone related medications, should be particularly alert to the risks of VTE and the signs and symptoms described above. Medical advice should be sought immediately in the event of any concerns.

(d) All medical practitioners need to be vigilant about the possibility of a VTE, even in situations where a patient appears to have no, or few, risk factors.

[44] Further, I note Dr McLintock's advice regarding recent studies which show emerging data of an association between vaping and the development of VTE, possibly due to activation of clotting cells called platelets or direct damage to lung blood vessels. Although Dr McLintock notes that data from large cohorts is not yet available, I strongly encourage medical practitioners, and people at increased risk of VTE, to be alert to these possible risks.

Distribution

[45] A copy of these findings and recommendations will be provided to Medsafe. I will also send a copy to the New Zealand Family Planning Association and the Royal New Zealand College of General Practitioners and will encourage those organisations to bring my conclusions and recommendations to the attention of their staff and members respectively. A copy will also be provided to the Ministry of Health.

Publication restriction

Under s 74 of the Coroners Act 2006 I prohibit making public any of the photographs of Isabella entered into evidence upon the grounds of personal privacy and decency. I am satisfied that such interests outweigh the public interest (if any) in the publication of those images.

Concluding remarks

[46] I wish to thank Isabella's parents for their significant assistance and patience during the course of this inquiry. The evidence I have reviewed indicates that Isabella was an exceptional and vibrant young woman who lived life to the full. She was also a cherished daughter and family member who had a bright and promising future ahead of her. Her sudden and premature death would have been devastating for her whānau and friends, particularly her twin brother, and I extend my deepest condolences to them all.

Coroner J Anderson