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香 港 醫 訊

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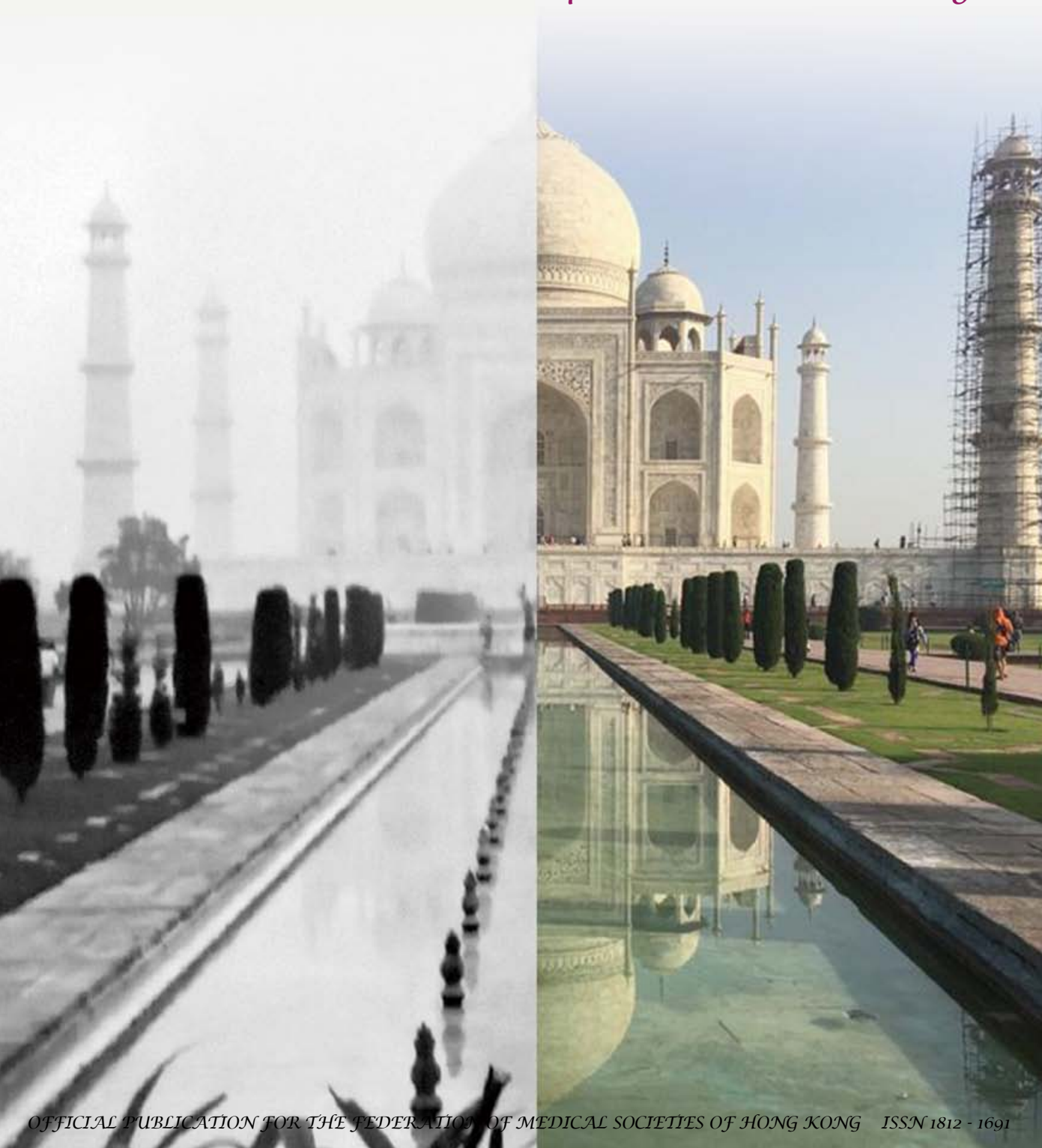
Massive Postpartum Haemorrhage



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Breast-feeding is the best form of nutrition for babies and provides many benefits to babies and mothers. It is important that, in preparation for and during breast-feeding, pregnant and lactating women eat a healthy, balanced diet. Combined breast and bottle-feeding in the first weeks of life may reduce the supply of their own breast-milk, and reversing the decision not to breast-feed is dicult. Always consult healthcare professional for advice about feeding baby. If infant formula is used, mothers / care givers should follow manufacturer's instructions for use carefully– failure to follow the instructions may make baby ill. The social and financial implications of using infant formula should be considered. Improper use of an infant formula or inappropriate foods or feeding methods may present a health hazard.

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Contents

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The Cover Shot

Taj Mahal 2003 (by Ms Deborah AUYEUNG)

Taj Mahal 2016 (by Ms Amanda CHUNG)

Eternal love – Taj Mahal is an ivory-white marble mausoleum in the Indian city of Agra. It was commissioned in 1632 by the emperor, Shah Jahan, to house the tomb of his beloved wife, Mumtaz Mahal, who died of massive postpartum haemorrhage, the theme of the current issue of HKMD. The two photos of Taj Mahal were taken in 2003 & 2016 by Deborah AuYeung & Amanda Chung respectively.

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An Overview on Massive Postpartum Haemorrhage in Hong Kong

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Editor

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Massive primary post-partum hemorrhage (PPH), as defined by a blood loss of >1,500 ml within the first 24 hrs after delivery, is an important cause of maternal morbidity & mortality. It has been chosen as the Clinical Indicator for Obstetric performance in Hospital Authority (HA) hospitals.

With the objectives of studying the characteristics of patients with massive primary PPH and exploring areas for improvement in terms of prevention & treatment, a prospective study was conducted during the year 2013 in all the 8 HA Obstetric Units using a pre-designed code sheet to record the details of all patients with massive primary PPH, including causes, risk factors, mode of delivery, interventions (uterotonic agents, second-line therapies and emergency hysterectomy), use of blood products, and maternal outcome[1].

Massive primary PPH occurred in 0.76% (n=277) of all deliveries (n=36,510) in HA Obstetric Units in 2013. The incidence was comparable to those reported in international literature. The majority occurred after Caesarean sections (84.1%). Uterine atony (37.5%), placenta praevia/ accreta (49.9%) & uterine wound bleeding/tear during Caesarean section (24.2%) were the 3 most common causes. The median total blood loss was 2,000 ml (range 1,500-20,000 ml). Coagulopathy occurred in 16.2% (n=45). A quarter (27.4%) (n=76) required Intensive Care or High Dependent Unit admission. There was no maternal mortality.

Second-line therapies (balloon tamponade, compression sutures and uterine artery/ internal iliac artery embolisation or surgical ligation) were used in 40.1% (n=111). Emergency hysterectomy was required in 8.7% (n=24). A total of 1,052 units of packed cells, 670 units of platelets, 568 units of fresh frozen plasma and 200 units of cryoprecipitate were transfused.

The study identified three areas for improvement: (1) to increase the choice of uterotonic agents (Carbetocin has been incorporated into HA Drug Formulary since January 2017, mainly for prevention of PPH in women at risk such as twin pregnancy, large fibroids, polyhydramnios, and prolonged induction of labour. In 2017, a total of 875 ampoules have been used in HA Obstetric Units, rising to 2,150 ampoules in 2018); (2) to step up the use (and early use) of second-line therapies, and to watch out for failures from second-line therapy ; (3) to reduce the incidence of placenta praevia/accreta through education and to improve its management at multiple care levels.

The pre-designed code sheet has been transformed into an electronic form (Figure 1) (available from January 2017) with multiple user-friendly functions in the HA Clinical Management System (CMS) to facilitate documentation, clinical audit & root cause analysis of patients with massive primary PPH. The usage of this CMS massive PPH electronic form was only 17% in 2017, increasing slightly to 20% in 2018. Obviously further design improvement as well as promotion on using this electronic form are necessary.

Maternal mortality related to massive PPH is rare in Hong Kong (touch

wood!). Nevertheless, isolated cases did occur over the years, both in HA and in private sector. I have had the opportunity to be involved as an expert witness in some of these medicolegal cases and have learned a lot. Even if the care provider has done nothing wrong, a good medical indemnity provider service is essential and can make a difference. In this regard, we cannot miss Dr Ares Leung's paper in the Lifestyle Section.

Both the concepts and therapeutic modalities in the clinical management of PPH have been revolutionised in the recent decade. This issue of the Hong Kong Medical Diary provides an excellent opportunity for us to illustrate the contemporary management of massive PPH. In Chapter 1, Dr Martin Lau, a promising upcoming O & G specialist, gives a concise summary on the current usage of various drugs in the prevention and treatment of massive PPH. In Chapter 2, Dr Frances Lui, an obstetric anaesthetist, explains the new concepts in haemostatic management of PPH. In Chapter 3, Dr Meliza Kong and Dr William To, who have extensively published on second-line therapies for PPH, describe the use of balloon tamponade and compression sutures, which have become an essential component in the algorithms for the management of PPH nowadays. In Chapter 4, Dr Danny Cho, an interventional radiologist and an essential partner to obstetricians in managing massive PPH, focuses on the use of uterine artery embolisation. In Chapter 5, Dr Menelik Lee writes on peripartum hysterectomy, which remains a life-saving operation in massive PPH when all the other measures have failed. In Chapter 6, Dr LL Chan, with her prior experience at Stanford University Medical School, gives us a thought-provoking discussion on PPH from a research perspective.

I am certainly indebted to all the authors / friends for their time and effort out of their busy schedules in preparing the manuscripts. But I am sure readers of the Hong Kong Medical Diary including our O & G specialists and trainees would find this issue informative and interesting.

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Fig. 1. HA CMS electronic form for massive PPH : Full data entry into (a), (b), (c) and (d) would lead to a print-out (e) and to automatic data incorporation for future analysis.

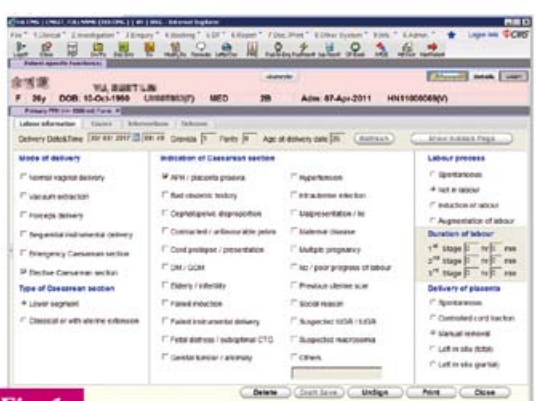

Fig. 1a

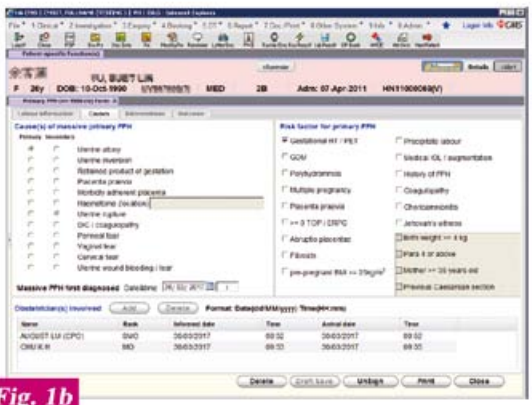

Fig. 1b

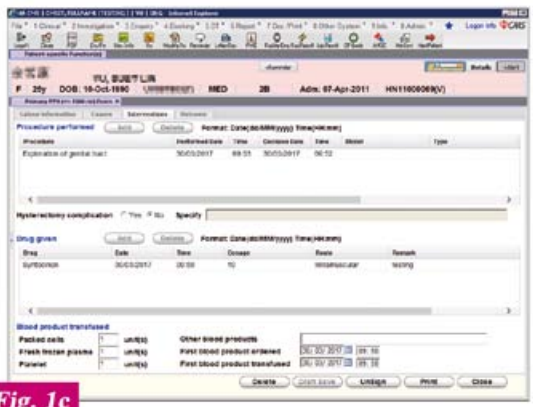

Fig. 1c

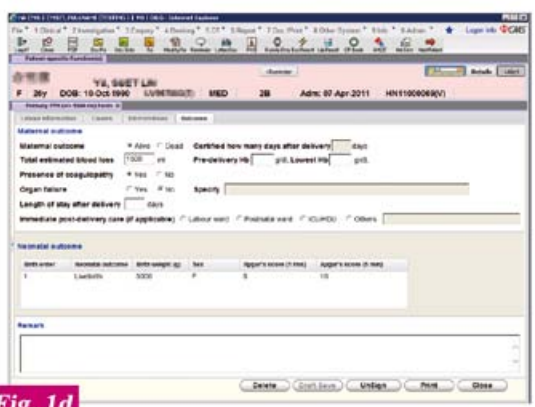

Fig. 1d

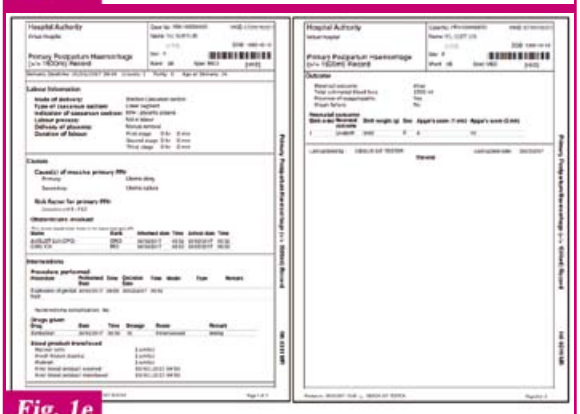

Fig. 1e

Contemporary Pharmacotherapy for Prophylaxis and Treatment of Massive Postpartum Haemorrhage

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Dr Martin KW LAU Dr Wing-cheong LEUNG

Postpartum haemorrhage (PPH) is an obstetric emergency with uterine atony being the most common cause[1]. Routine prophylactic use of uterotonic drugs can reduce the risk of PPH by 50% in the overall obstetric population[2]. Active management of the third stage of labour can reduce the risk of PPH of ≥ 1,000 ml[3], with the use of oxytocics being one of the three pillars of the active management of third stage, and the other two being early cord clamping and controlled cord traction[3].

The choice of medication for prophylaxis and treatment for massive PPH can be broadly classified into uterotonics and non-uterotonics. In Hong Kong, there are four uterotonic medications currently licensed for prophylaxis or treatment for PPH:

1) synthetic oxytocin (Syntocinon®);
2) fixed-dose combination of synthetic oxytocin with ergometrine (Syntometrine®);
3) synthetic prostaglandin analogue of PGF2α - carboprost (Hemabate®);
4) synthetic peripheral oxytocin receptor agonist of carbetocin (Duratocin®).

In addition, there is off-label use of the synthetic prostaglandin analogue of misoprostol (Cytotec®) in the treatment of PPH. Ergot Alkaloids of ergometrine is registered in HK, but it is only available in the oral form and is not used for the prophylaxis or treatment of primary/massive PPH, while sulprostone (Nalador®) was withdrawn from HK after overseas case reports of acute myocardial infarction following its use.

SYNTHETIC OXYTOCIN

Being the most widely used oxytocic, synthetic oxytocin (SO) structurally resembles its natural form as a hormone. Apart from the use as a labour induction agent, SO can reduce PPH and the need for therapeutic uterotonics by more than 40% (blood loss of ≥ 500 ml, RR 0.53; need for therapeutic uterotonics, RR 0.56)[2]. The intravenous administration has an immediate onset of action to reduce the risk of PPH of ≥ 1,000ml by half[4]. Nonetheless, its short biological half-life of three to five minutes[5] requires a continuous intravenous infusion for a sustained effect. Due to its nature of being a hormone, SO carries minimal contraindications as compared with the other uterotonics. There is a < 3% risk of tachycardia and hypotension associated with its use, but the risk of cardiovascular collapse may increase[6] if an intravenous bolus regimen is used in the patients with neuraxial anaesthesia. Further caution should be taken for its use in massive PPH as the patient may already be in a state of hypovolaemia.

OXYTOCIN WITH ERGOMETRINE

The fixed-dose combination of synthetic oxytocin with ergometrine (Syntometrine®) is an intramuscular injection that contains five units of synthetic oxytocin and 0.5 mg of ergometrine. It can be easily administered without the need for intravenous access, with the onset of uterotonic effect in three minutes and a sustained uterotonic effect lasting three hours[7]. It is effective in the prevention of PPH, but a systemic review has shown that it has no additional benefits in the treatment for PPH of ≥ 1,000 ml[8]. Due to the ergometrine ingredient, it carries the side effects of causing an increase in blood pressure, headache and vomiting[4]. It is also contraindicated in patients with asthma, valvular heart disease and severe hypertension[9], which are not uncommon medical conditions in the modern obstetric population.

CARBOPROST

The synthetic prostaglandin analogue of PGF2α – carboprost (Hemabate®) is a solution that contains 250 micrograms of carboprost. It can be administered as an intramuscular or intramyometrial injection for the treatment of PPH refractory to conventional methods of treatment using oxytocic agents and/or ergometrine. The prophylactic use is not associated with the prevention of PPH of ≥ 1,000 ml[4]. It is contraindicated in patients with active cardiac disease or asthma.

CARBETOCIN

The synthetic peripheral oxytocin receptor agonist of carbetocin (Duratocin®), is a single dose agent that contains 100 micrograms of carbetocin, with the oxytocic activity of 50 units of oxytocin. It is indicated for the prevention of uterine atony after Caesarean section and is administered as a slow intravenous injection over one minute, with a rapid onset of uterine contraction within two minutes and lasting for several hours. It is effective in the prevention of PPH of ≥ 1,000 ml. It is a heat-stable compound that does not require refrigeration. The side effect profile is similar to synthetic oxytocin[10], though caution should be taken for patients with vascular disease, and especially coronary artery disease. Carbetocin has been widely used in the private sector in Hong Kong because of its efficacy. It has also been

recruited into the Hospital Authority (HA) Drug Formulary since 2017, mainly for prevention of PPH in those women with risk factors such as twin pregnancy, large fibroids, polyhydramnios, prolonged induction of labour and others. In 2017, a total of 875 ampoules have been used in HA Obstetric Units, increasing to 2,150 ampoules in 2018.

MISOPROSTOL

Unlike the previous four medications, misoprostol is not licensed for obstetric or gynaecological purposes in Hong Kong although it has been used extensively. It is less effective than the injectable uterotonics[11], with a limited role for the prophylaxis and treatment of massive PPH. However, being a heat-stable compound and its tablet form allowing ease of administration to various mucosal cavities have rendered Misoprostol an effective drug in the low-resource area and where intravenous access is not available.

NON-UTEROTONIC AGENT – TRANEXAMIC ACID

In terms of non-uterotonic agents, tranexamic acid is an antifibrinolytic agent with a long history of use in the prevention and treatment of bleeding in various conditions and with an excellent safety profile. Following a Cochrane review[12], the Royal College of Obstetricians and Gynaecologists recommended the use of intravenous tranexamic acid as PPH prophylaxis in addition to synthetic oxytocin during Caesarean sections for women at increased risk of PPH[13]. From a treatment perspective, based on the established effectiveness in management of trauma[14], the multicentre WOMAN—World Maternal Antifibrinolytic—trial[15] has demonstrated the effectiveness of tranexamic acid in reducing death due to PPH by 20 to 30% without adverse events including venous thromboembolism, and it should be given as soon as possible after onset of bleeding. In high-risk patients, consideration should be given to infuse one gram of tranexamic acid intravenously, followed by a second dose 30 minutes later if required.

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Haemostatic Management of Postpartum Haemorrhage

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 July 2019.

Postpartum haemorrhage is one of the leading causes of maternal mortality worldwide. Effective management is mandatory to save lives and improve patient outcome, starting from antenatal risk management, early control of bleeding, optimising haemostasis to maintenance of haemoglobin and oxygen delivery (Fig. 1). This article briefly reviews recommended strategies to optimise haemostasis based on recent evidence and consensus. It must be emphasised that education, drills and audits are required to ensure successful implementation of strategies.

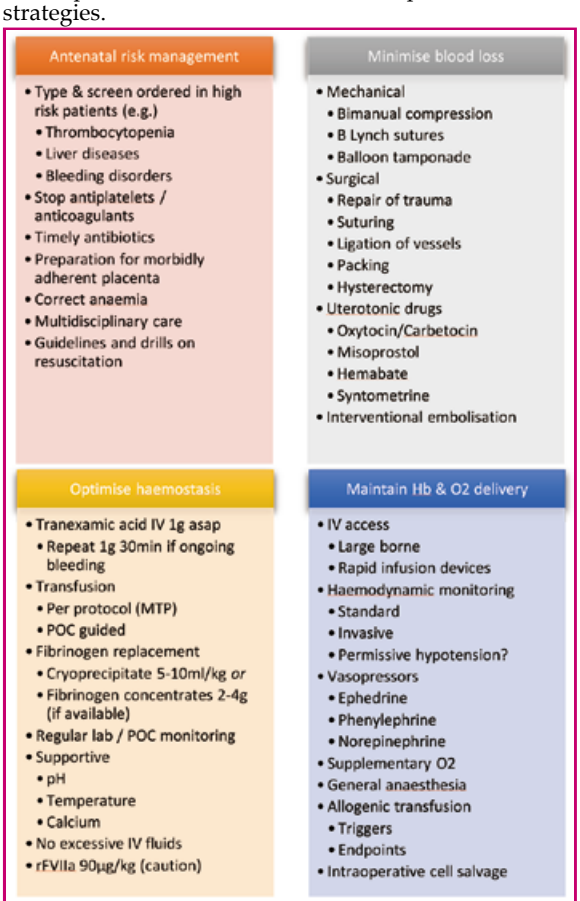

Fig.1. Overview of PPH management. Periodic evaluation of clinical response and escalation of care if required is mandatory for all pillars. The pillar on "optimising haemostasis" summarises this review hence elaborated. See text for details.

Normal pregnancy is associated with venous stasis, endothelial adaptation and hypercoagulability. Circulating plasma volume increases. Levels and activities of natural pro-coagulants (factors V, VII, VIII, IX, von Willebrand's factor (vWF) and fibrinogen) increase while anti-coagulants (proteins S) decrease; the extent of all these changes correlate in general with the gestational age. Fibrinolysis is depressed as a result of the increased thrombin activatable fibrinolysis inhibitor (TAFI) and the production of plasminogen activator inhibitors (PAI-1 & 2) by the placenta, but fibrinolysis is quickly normalised and may at times overshoot in postpartum days. D-dimer increases progressively and peaks at day one postpartum. Activated thromboplastin time (aPTT), Prothrombin time (PT), activated protein C and thrombomodulin levels generally remain unchanged.[1,2] The delicate balance between coagulation and fibrinolysis highlights the dilemma in the cessation of postpartum haemorrhage and subsequent risk of thromboembolism.

Fibrinogen rises from non-pregnant level to 3.1 g/L (median) in the first trimester and further to 4.8 g/L at term, as validated in the Chinese.[3] A reduced fibrinogen had been shown as an independent predictor of progression of severe postpartum haemorrhage, and the need for invasive procedures, embolisation, transfusion requirements and intensive care admission.[4] This has significant implication in the goal-directed approach of transfusion, timely fibrinogen replacement and early administration of anti-fibrinolytic drugs in treating haemostastic failure in massive postpartum haemorrhage.

Gestational thrombocytopenia (platelet count less than 150,000/μL) affects about 10% of all pregnancies with most occurrences in the third trimester.[5] The count seldom falls below the critical level or requires treatment as clot formation is compensated by raised vWF and fibrinogen level. In the absence of pregnancy-related disorders such as pre-eclampsia, auto-immune causes, or anticipated invasive procedures, prophylactic platelet transfusion is not required. In postpartum haemorrhage, it is recommended that platelet counts should be maintained at more than 75,000/μL.

There is a misconception that postpartum haemorrhage is always associated with disseminated intravascular coagulation (DIC). Genuine DIC is very rare in obstetrics. In uterine atony and genital tract trauma, which account for 80% of primary postpartum haemorrhage, fibrinogen, PT and aPTT are normal even after 1,500 ml of blood

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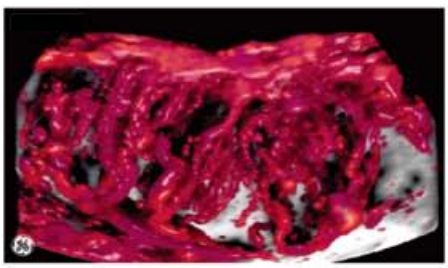
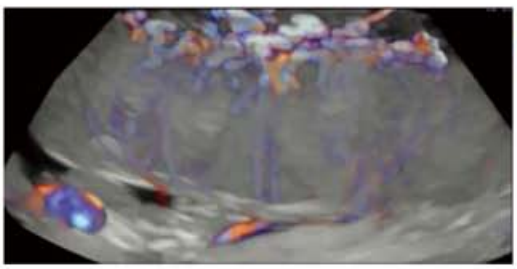


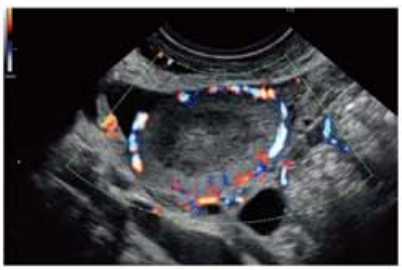
HDlive flow

To present vascular structures with greater anatomical realism



Glass Body Mode

To display transparent tissue and color vessel information



HDFlow

Excellent color sensitivity that gives a detailed vasculature

has been lost. It is only when bleeding is not stopped and excessive fluid has been administered for shock, that eventually dilutional coagulopathy develops, leading to reduced thrombin generation, fibrinogen and hence clot strength.[6] In placenta abruption with concealed bleeding or retained product of gestation, coagulopathy can develop early on since placental separation is usually localised to the placental bed rather than "disseminated". Only fibrinogen and platelet are consumed without significant deficiency in other coagulation factors. Sepsis and amniotic fluid embolism are the two conditions associated with genuine DIC where platelets and coagulation factors are profoundly consumed to below critical levels with diffuse activation of fibrinolysis and microvascular thrombosis. Anti-fibrinolytic drugs are contraindicated due to risk of widespread fibrin deposition.

Laboratory coagulation screen, platelet count and Clauss assay of fibrinogen take a long turnaround time to aid diagnosis of coagulopathy and guide transfusion strategies in emergency. Point-of-care tests including platelet function assays (impedence aggregometry e.g. PFA-100/-200) and viscoelastic tests (thromboelastography (TEG®), thromboelastometry (ROTEM®)) performed on the whole blood have been explored. In addition to a faster turnaround time, viscoelastic tests provide comprehensive information on clot initiation, propagation and lysis through graphical display at the patient's bedside. The use of TEG® or ROTEM® to monitor haemostatic treatment in critical bleeding has been reviewed by Cochrane with reduction in transfusion requirements demonstrated but the majority of trials included were conducted in cardiac surgery patients.[7] Utilisation of POC in developing transfusion algorithm in postpartum haemorrhage is a rapidly expanding research area. In particular, the FibTEM test of ROTEM® provides data on "functional" fibrinogen on clot formation. In an observational cohort (n=605) of women with postpartum haemrorhage with median total blood loss of 1,500 ml, 98% of fresh frozen plasma (FFP) transfusion was withheld when the FibTEM A5 (clot amplitude measured at 5 minutes) was over 15 mm persistently.[8] In those (n=55) who had ongoing bleeding and FibTEM A5≤15 mm, they were further randomised to receive fibrinogen concentrate or placebo. It was concluded that fibrinogen concentrate was not required when ROTEM FibTEM A5 was >12 mm or when the Clauss fibrinogen was >2-2.5 g/L.[9] It is likely that a restrictive transfusion strategy as guided by POC viscoelastic tests is feasible. However, POC tests with expertise in its use are not widely available in delivery suites in Hong Kong. Until then conventional laboratory tests should be done regularly to guide transfusion as the standard of care.

In major bleeding, ordering blood and blood components separately is time consuming. Massive transfusion protocol (MTP) is a bundle approach rooted from adult trauma resuscitation to issue transfusion packs in a formula-based fixed ratio of packed red blood cells to fresh frozen plasma (PRBC:FFP), with or without cryoprecipitate and apheresis platelets. Once activated through pre-defined clinical or laboratory criteria, clinical staff, blood bank, laboratory support and porter service are all mobilised with improved lines of communication. In a recent review comparing bleeding trauma patients, there was no difference in mortality and morbidity with either PRBC:FFP:platelets in 1:1:1 or 2:1:1 transfusion ratio.[10] The optimal dose, ratio and timing of blood components have never been established. The configuration for obstetric haemorrhage is likely different due to a hypercoagulable state and raised plasma volume at term with increased tolerance to considerable anaemia. In addition, uterotonic drugs and Caesarean hysterectomy are options in treating critical atonic haemorrhage but not adult major trauma. The American College of Obstetricians and Gynecologists (ACOG) recommended either 1:1:1 or 1:2:4 ratio.[11] The green top guideline of the Royal College of Obstetricians and Gynaecologists (RCOG)[12] recommended FFP 12-15 ml/kg after 4 units of PRBC or in suspected coagulopathy to maintain PT/aPTT at <1.5 times normal, and cryoprecipitate infusion to maintain fibrinogen >2 g/L. With the increasing popularity of POC coagulation assay, it is likely a goal-directed transfusion algorithm would replace a formula fixed ratio MTP approach in the future.

FFP had been used traditionally to correct "coagulopathy" associated with postpartum haemorrhage but is now known to be "incorrect". As discussed, 80% of postpartum haemorrhage are associated with uterine atony without baseline coagulopathy and only require fibrinogen replacement. Furthermore, most coagulation factors are already increased at term gestation. FFP on average contains 2 g/L of fibrinogen, whereas the term pregnant level is on the average 4 g/L. Hence, using FFP to correct hypofibrinogenaemia would only further dilute fibrinogen level particularly when given as fixed ratio approach.[4] FFP transfusion is also associated with transfusion-related lung injury and circulatory overload.

Cryoprecipitate is prepared by thawing FFP between 1-6°C, centrifugation and resuspension of the precipitated proteins. It contains a much higher concentration of fibrinogen in a relatively small volume, with each unit containing a variable amount of fibrinogen. In addition, cryoprecipitate contains Factors VIII, XIII, vWF and fibronectin. As multiple units are usually required, it carries a greater risk of viral transmission although each unit is donated by a single donor. In many countries cryoprecipitate is not used due to safety concern. In Hong Kong, cryoprecipitate is currently the only available option for fibrinogen replacement except in treating patients with congenital fibrinogen deficiency or dysfibrinogenaemia.

Fibrinogen concentrate is produced from pooled human plasma but processed to reduce viral transmission as well as removal of blood group matching. It is a lysophilised powder stored at room temperature and only requires reconstitution, unlike cryoprecipitate which requires ordering and thawing. The simplicity, ease and speed in emergency administration had prompted the fibrinogen concentrate to become the preferred source of fibrinogen replacement in many countries despite off-label use in obstetric haemorrhage. Both fibrinogen concentrate and cryoprecipitate appear equally efficacious in raising plasma fibrinogen concentration when dosed appropriately. What remains unclear is the treatment target for fibrinogen replacement, given that most term pregnant women have a higher baseline level.[13]

Table 1. Comparison of different sources that give equivalent dose of 4 g fibrinogen

	Fresh frozen plasma	Cryoprecipitate	Fibrinogen concentrate
Equivalent unit(s)	8 units	~12 – 27 units (usually administered in packs of 5 to 10 units)	4 g (70 mg/kg for 57 kg adult, dose adjustment if fibrinogen level is known)
Fibrinogen concentration (g/L)	2	10 - 21 (150-325 mg each unit)	20
Volume (mL)	1600 (~200 ml each)	400 (~15 ml each)	50 (reconstituted with water for injection)
Manufacturing source	Single donor each	Single donor each	Pooled human plasma
Cost	$	$$	$$$$
Viral inactivation	No	No	Yes
Storage	-30°C	-30°C	Room temperature for unopened vial
Thawing before administration	37°C for 20 min then stored at room temperature, must be transfused within 4h	37°C for 20 min then stored at room temperature, must be transfused within 4h	Not required
Blood group compatibility	ABO & Rh	ABO suggested	Not required
Remarks	Aggravate hypofibrinogenaemia due to dilution	Also contains vWF, FVIII, XIII, fibronectin, A2-AP, microparticles	Not available in HK

Tranexamic acid is an anti-fibrinolytic that inhibits the breakdown of fibrinogen and fibrin by plasmin. The use of intravenous tranexamic acid has been studied in the multicentre WOrld Maternal ANtifibrinolytic (WOMAN) trial (n=20060) and reviewed by Cochrane. Intravenous tranexamic acid 1 g reduced risk of maternal death due to bleeding in primary postpartum haemorrhage without adverse effects (RR 0.81, 95% CI 0.65-1.00). However, treatment must be given as soon as possible after onset and was ineffective after 3 hours. A second dose can be given after 30min if needed. It did not reduce the risk of serious morbidities, hysterectomy nor blood transfusion.[14] In another meta-analysis (n=4671), prophylactic tranexamic acid 1 g given 10 minutes after vaginal delivery also reduced risk of PPH (RR 0.61 95% CI 0.41-0.91) with a mean lower blood loss (MD -84.74ml) without thromboembolic events.[15]

The RCOG guideline[12] recommended infusion up to 3.5 L of warmed clear fluid with initial 2 L of crystalloid until blood is available. The Transfusion strategies in Women during Major Obstetric Haemorrhage (TeMpOH-1) study is a national retrospective multicentre cohort study in the Netherlands (n=883).[16] Women who received over 4 L of clear fluids (crystalloids, colloids or both) before the start of red cells transfusion suffered more adverse maternal outcomes than women in the reference group, with deterioration in coagulation parameters corresponding to dilution.[17] If fluid is required for expanding plasma volume, buffered fluids containing bicarbonate or its precursor (such as gluconate, lactate or acetate) and electrolytes matched closely with plasma are probably better in reducing hyperchloraemia and metabolic acidosis in surgical patients.[18] It should also be noted that calcium is contained in some (e.g. Lactated Ringer's, Hemaccel) but not in other fluids (e.g. Normal saline, Gelofusine). Body temperature, pH and calcium are important physiological prerequisites for proper enzymatic functions of coagulation factors.

The use of rFVIIa in obstetric haemorrhage remains an off-label use with controversies. The Australian and New Zealand Haemostasis Registry included 177 patients with obstetric haemorrhage from year 2000 to 2009[19]. The median dose given was 90 μg/kg and most patients received a single dose. Bleeding was reduced in some but not all patients. pH and clinical context are more important factors associated with likelihood of reduction in bleeding and death. Subgroup analysis of these 177 obstetric patients showed 8.6% thromboembolic events. The Japanese registry studied 69 patients treated with rFVIIa with mean blood loss 11,835 ml.[20] 65 patients survived. 4 had thromboembolic events. Echoed with the Australian registry, survival correlates more with the underlying clinical condition rather than the amount of blood loss. The RCOG guideline[12] suggested rFVIIa only in clinical trials and after correction of hypothermia, acidosis and low platelets as physiological prerequisites.

PCC contains vitamin K-dependent clotting factors, and protein C and S and has been used in urgent reversal of vitamin K antagonists or direct oral anticoagulant-induced bleeding. There are insufficient data to support its use in obstetrics due to the risk of thrombosis and transmissible disease as a pooled donor product.

Haemostatic management of postpartum haemorrhage should be aetiology-based and goal-directed. Majority of women develop dilutional coagulopathy with ongoing bleeding and fluid resuscitation. Fibrinogen is depleted rapidly and the rate of depletion correlates with progression of haemorrhage. It should be replaced by either cryoprecipitate or fibrinogen concentrates but not fresh frozen plasma. Intravenous tranexamic acid should be given as soon as possible after onset of bleeding to improve patient outcomes. Hypothermia, acidosis and hypocalcaemia must be corrected before considering recombinant factor VIIa as the last resort. Point-of-care viscoelastic assay shows promising evidence to guide transfusion strategies but requires expertise and is not widely available in delivery suites in HK. Massive transfusion protocol with a fixed ratio of blood and components remains the standard of care at present moment.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Haemostatic Management of Postpartum Haemorrhage" by Dr Frances LUI and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 July 2019 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Pregnancy is a physiological hypercoagulable state.**
2. **The level of fibrinogen increases with gestation to almost double at term. Level correlates with progression of severe postpartum haemorrhage.**
3. **Uterine atony is not a common cause of primary postpartum haemorrhage.**
4. **In massive postpartum haemorrhage, fresh frozen plasma should be used to replace fibrinogen level. Either cryoprecipitate or fibrinogen concentrate should be used instead of FFP.**
5. **Tranexamic acid should be given 1g intravenously as soon as possible after the onset of haemorrhage.**
6. **Recombinant factor VIIa should be given 90 μg/kg intravenously as soon as possible after the onset of haemorrhage.**
7. **Excessive infusion of intravenous fluid to treat hypovolaemic shock is associated with dilutional coagulopathy and further reduction in fibrinogen level.**
8. **The transfusion of blood and blood components in an empirical ratio of PRBC:FFP:Platelet 1:1:1 had been shown to improve patient outcomes in treating obstetric haemorrhage.**
9. **Prevention of hyperthermia is important in maintenance of haemostatic function.**
10. **Laboratory assay of coagulation screen and fibrinogen is associated with longer turnaround time than point-of-care assay but should still be performed in massive postpartum haemorrhage.**

ANSWER SHEET FOR JULY 2019

Please return the completed answer sheet to the Federation Secretariat on or before 31 July 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Haemostatic Management of Postpartum Haemorrhage

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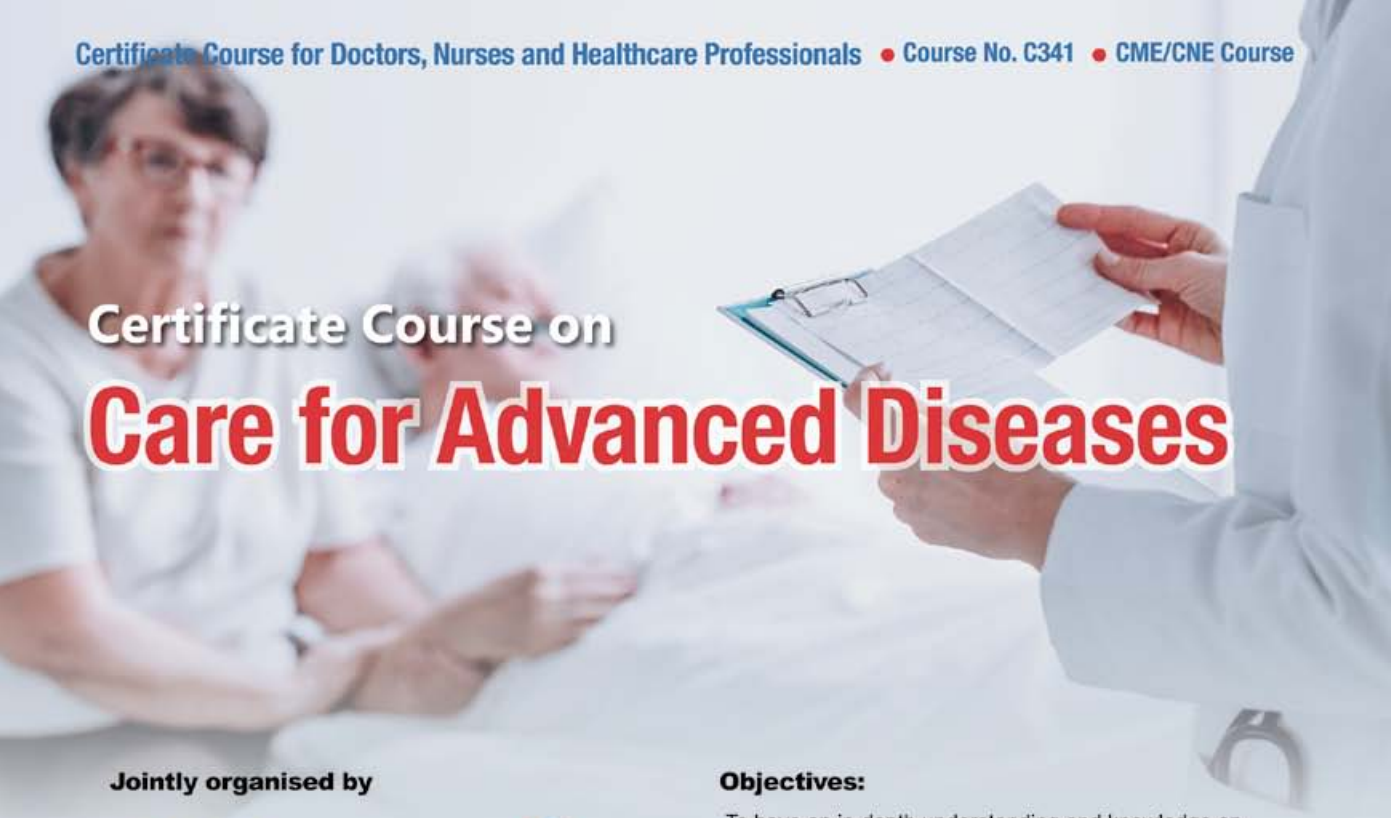
Contact Tel No.:_____ MCHK No.: _____ (must fill in)

Answers to June 2019 Issue

Hypercholesterolaemia: From Public Health Perspective to Patient Care

1. T 2. F 3. F 4. T 5. F 6. F 7. F 8. F 9. T 10. T

Certificate Course for Doctors, Nurses and Healthcare Professionals • Course No. C341 • CME/CNE Course



Certificate Course on
Care for Advanced Diseases

Jointly organised by

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Objectives:

To have an in-depth understanding and knowledge on Care for Advanced Diseases

Date	Topics	Speakers
15 Jul	Symptom control for advances diseases: applying principles to practice	Dr. Raymond Lo Specialist in Geriatrics Medicine
22 Jul	Counselling and support for patients and families facing advanced diseases: how to proceed	Dr. Cecilia Kwan Nurse consultant, Palliative Care
29 Jul	Advance Care Planning when facing serious illnesses: facilitating communication and decision making	Dr. Leung Man Chung Hospice Physician
5 Aug	Legal aspects in advanced diseases: Mental Health Capacity and Advance Directive	Dr. David Kan Solicitor
12 Aug	Dying at place of choice: enabling peaceful home deaths	Dr. Leung Man Fuk Specialist in Geriatrics Medicine

Dates : 15, 22, 29 July & 5, 12 August, 2019 (Every Monday)
Time : 7:00 pm – 8:30 pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
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Second-line Therapies – Balloon Tamponade and Compression Sutures

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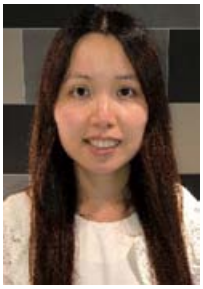


Dr Meliza CW KONG Dr William WK TO

INTRODUCTION

Postpartum haemorrhage (PPH) continues to be one of the world's leading causes of maternal mortality. The basic treatment of severe PPH consists of medical management by uterotonic drugs such as oxytocin, and prostaglandin or their analogues. Traditionally, peripartum hysterectomy would be performed in patients with massive PPH as a life-saving rescue procedure in those who failed to respond to uterotonics. However, the morbidity associated with peripartum hysterectomy can be high, with risks of further intraoperative blood loss, adjacent organ injury, coagulopathy, need for massive blood product transfusion, postoperative haemorrhage and wound complications, as well as other medical complications such as venous thromboembolism. In addition, hysterectomy is also obviously associated with permanent loss of future fertility. Therefore, various conservative surgical procedures have been developed in recent years to reduce the need for hysterectomy, including intrauterine balloon tamponade, external compression sutures, selective de-vascularisation by surgical ligation or radiological embolisation of the uterine and pelvic arteries[1-3]. In recent decades, these second-line conservative surgical procedures have been gradually incorporated into protocols for severe PPH management[4]. The effectiveness of these conservative second-line procedures in reducing the incidence of hysterectomy has recently been demonstrated in several large international epidemiological studies[5,6], as well as in our local studies[7,8].

BALLOON TAMPONADE

The Different Types of Uterine Balloons

Application of intrauterine pressure to produce an internal compression effect to control PPH from balloon tamponade has probably evolved from uterine packing. The first description of such tamponade technique by uterine packing with cotton gauze to manage PPH has been ascribed to the literature dating back to year 1855[9]. Over time, different hydrostatic balloons such as condom balloon, Foley catheter balloon, Sengstaken–Blakemore gastro-intestinal tube, and Rusch balloon were used for uterine tamponade as they were easier and quicker to be placed than the traditional uterine packing. Subsequently, uterine specific balloons such as the Bakri balloon (Fig. 1), BT- catheter or Belfort-Dildy Obstetrical Tamponade System systems were introduced. The theoretical advantage of the uterine-specific balloons is that they can conform to the intrauterine cavity once inflated and therefore may have a lower expulsion rate or perforation rate.

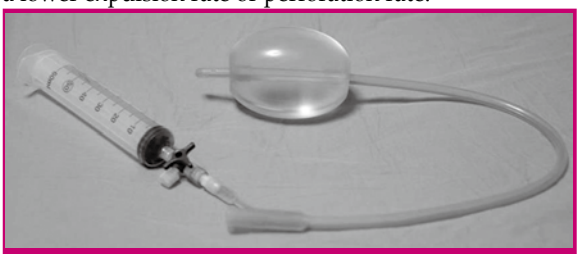

Fig. 1. Intrauterine balloon tamponade device – Bakri balloon There is a two-way catheter for saline infusion into the balloon and drainage from the uterine cavity.

The Efficacy of Uterine Balloons to Manage PPH

Both uterine-specific and non-specific balloons have in general reported a high success rate despite wide discrepancies in their costs. An early case series described the use of a Foley catheter inserted into the uterine cavity in 20 patients for control of PPH as well as for acute haemorrhage from the non-puerperal uterus, and the procedure was completely successful in 17 patients and partially successful in 2 patients[10].

Condom catheter has been shown to have a generally high success rate in treating PPH in developing countries. A review of the effectiveness of intrauterine balloon tamponade for the treatment of PPH in resource-poor settings identified 13 studies in which the condom catheter was used in around 95% of the cases, and was shown to be successful in treating the PPH in 234 out of 241 women [11].

A prospective observational intervention study was conducted with the Bakri balloon over a 29-month period in Kenya for women diagnosed with PPH unresponsive to standard intervention. PPH was controlled without further surgical intervention in 95% of patients (55/58)[12]. Another Finnish series reported 44 women with massive PPH (blood loss >1,000 mL) and 6 other women with expected high risk of PPH (blood loss <1,000 mL) managed by the Bakri balloon. The overall success rate was 86% and 7 of the 50 patients needed additional procedures. Among these failures, supra-vaginal uterine amputation or hysterectomy was required in four cases and embolisation of the uterine arteries in three other cases. The authors concluded that even if Bakri balloon failed, it might provide temporary tamponade and time

to prepare for other interventions or transportation from local hospitals to a tertiary centre [13].

An Egyptian study attempted to assess the efficacy and safety of condom-loaded Foley catheter versus Bakri Balloon in the management of primary atonic PPH secondary to vaginal delivery in a single-blind randomised controlled trial. Both balloon catheters were found to successfully control the PPH without statistically significant difference. However, Bakri balloon required shorter time to stop the uterine bleeding than a condom-loaded Foley catheter (9.09 min vs. 11.76 min, p=0.042). There was no difference between both groups regarding postpartum maternal complications, or other vital signs such as urine output or haemoglobin levels[14]. Apart from this study, there are apparently no other direct head-on comparison data of the efficacy of different intrauterine balloon systems available in the literature. Nevertheless, balloon tamponade has been shown to have high efficacy in the management of PPH.

COMPRESSION SUTURES

The Different Types of Compression Sutures

The first case report of uterine compression sutures was published in 1996 with a single patient from Zurich[15]. B-Lynch et al published a case report of five consecutive cases utilising the B-Lynch suture in 1997[16]. (Fig. 2) Various modifications of the B-Lynch suture, and various other compression suture techniques have been reported since then. In 2000, Cho et al described a haemostatic multiple square suture to approximate the anterior and posterior uterine wall[17]. In 2002, Hayman et al proposed a uterine compression suture that involved two vertical apposition sutures together with two transverse horizontal cervico-isthmic sutures[1]. In 2005, Hwu et al described the use of two parallel vertical compression sutures placed in the lower segment to control bleeding from placenta praevia[18]. These kinds of compression sutures require additional laparotomy in case of vaginal deliveries. Therefore it is less commonly performed in patients with vaginal deliveries as their first second-line procedures compared with uterine balloon tamponade.

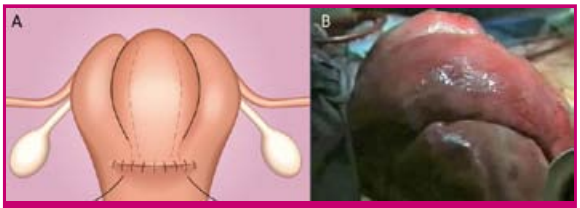

Fig. 2. Compression sutures – B-lynch suture
A. shows how to apply the B-lynch suture in the uterus
B. shows the B-lynch sutures in a real patient

The Efficacy of Compression Sutures to Manage PPH

A review article in 2013 summarised the findings of 11 original articles on compression sutures and found the success rate of compression sutures to stop bleeding ranged from 76 to 100% while B-Lynch sutures was the most widely performed[19]. However, there are no studies comparing an individual compression suture with other types of suture available in the literature.

The Use of Balloon Tamponade in Conjunction with Compression Sutures

The application of uterine compression sutures in conjunction with balloon tamponade are described as 'uterine sandwich'. A series of 11 patients with placenta praevia or uterine atony, in whom Hayman sutures combined with the Bakri balloon were applied, have been described with no major complications with 100% success rate[20]. In another series of 20 patients in whom the Bakri balloon was used as the treatment of first choice, 12 were successfully managed with the balloon alone but 6 warranted the balloon and B-Lynch sutures together, while two finally had a hysterectomy[21].

Complications from Balloon Tamponade and Compression Sutures

Different complications from balloon tamponade and compression sutures have been reported. Caesarean scar dehiscence has been found in balloon tamponade placement after a second-trimester dilatation and evacuation[22]. Uterine necrosis, pyometra and uterine synechiae had been found after application of uterine compression sutures[23-25]. In a case report, ten weeks following application of uterine compression sutures combined with Rusch intrauterine balloon, uterine necrosis ensued and hysterectomy was required[26]. The authors suggested looking out for uterine blanching when applying such balloon/sandwich techniques.

Comparison of Balloon Tamponade and Compression Sutures with Other Second-line Procedures

In a systematic review of various conservative management modalities for postpartum haemorrhage, estimated cumulative outcomes showed success rates of 91% for arterial embolisation, 84% for balloon tamponade, 92% for uterine compression sutures, and 85% for iliac artery ligation or uterine de-vascularisation. Nevertheless, the authors commented that balloon tamponade was the least invasive and most rapidly implemented, and that it seemed logical to use it as the first step of management in suitable patients[2]. There are little direct data available in the literature to compare the efficacy of different second-line conservative management for PPH. Randomised controlled trials would be difficult to perform in such life-threatening clinical scenarios presenting as a dire emergency. A fair comparison of the different treatment modalities would also be difficult to carry out, as specific treatments may be indicated in specific situations. For instance, uterine balloons may be particularly indicated for massive PPH after a vaginal delivery, while uterine compression sutures tend to be used (with or without balloon tamponade) after Caesarean delivery and while radiological methods for uterine artery embolisation depend on the availability of expertise of

an interventional specialist. It is therefore apparent that the use of these different modalities should be flexible and geared to the aetiology of the PPH and feasible clinical responses tailored to the condition of the patient concerned during different stages of the emergency.

Can Balloon Tamponade and Compression Sutures Reduce Peripartum Hysterectomy?

The impact of the increasing use of second-line procedures for the management of severe PPH on peripartum hysterectomy rates have been demonstrated in various studies worldwide. The use of second-line therapies including balloon tamponade, uterine compression sutures, pelvic vessel ligation and interventional radiology and Factor VIIa have been shown to be successfully in 74% of PPH patients without the need of peripartum hysterectomy[6]. Moreover, an analysis on peripartum hysterectomy trends over 4 decades in Dublin showed that the peripartum hysterectomy rates decreased from 0.9/1000 to 0.2/1000 from 1966-1975 to 1996-2005. The authors commented that apart from placenta accreta becoming the increasingly important indication for hysterectomy from 5.4% to 46.5%, hysterectomy for uterine atony has decreased over the decades and was most likely related to the use of conservative management including uterotonics agents, embolisation, uterine balloons, compression sutures and devascularisation[5]. The rising trend in the use of second-line therapies with decrease in peripartum hysterectomy was also observed in Hong Kong. In a 5-year local cohort from 2006-2011, it was shown that second-line procedures were used in around 46% of cases of massive PPH, and only 21.4% of the women who received second-line therapies would require rescue hysterectomies[7].

Specifically focussing on the impact of the use of balloon tamponade to manage severe PPH that was unresponsive to prostaglandins, a French cohort compared 2 equal periods before and after the introduction of this technique. The success rate with the Bakri balloon was 86%, and the rates of arterial embolisation and other conservative surgical procedures decreased from 8.2% and 5.1% in the first period to 2.3% and 1.4% in the second period respectively. While hysterectomy rates decreased non-significantly from 1% to 0.46% in the two periods, the authors commented that intrauterine balloon was an effective strategy for achievement of haemostasis in severe PPH[27]. This finding was also observed in Hong Kong. In a large local cohort spanning 16 years, the utilisation of uterine balloon tamponade increased from 0% at first to 48.8% in the last 4 years, and the overall percentage that had second-line conservative procedures increased from nil to around 83%. The total mean hysterectomy rate per quadrennium was also observed to fall significantly from around 1/1,000 deliveries to 0.6/1,000 (p=0.04) and the peripartum hysterectomy rate also dropped from 40% to 10% in all cases of severe PPH (p=0.04) [8]. Thus, with the increasing use of balloon tamponade as the first second-line procedure in recent years, both the utilisation of other second-line procedures and the need for peripartum hysterectomy have significantly been reduced.

CONCLUSION

The use of balloon tamponade and uterine compression sutures in the management of PPH carries high efficacy and can reduce the need and complications of peripartum hysterectomy. Complications from balloon tamponade and compression sutures are rare but should be taken note of especially when they are used in conjunction. As balloon tamponade is easy and quick to apply and can be used in both vaginal deliveries and Caesarean sections without expertise, it is now the first second-line treatment in many units in the world as well as in Hong Kong.

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Uterine Artery Embolisation in Managing Massive Postpartum Haemorrhage

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INTRODUCTION

Postpartum haemorrhage (PPH) is an obstetric emergency with significant maternal mortality and morbidity. It accounts for 27% of all maternal deaths worldwide.[1] Uterine artery embolisation (UAE) was first described in 1979,[2] and is now a well-established endovascular treatment option for PPH patients.[3] Compared with conventional hysterectomy, it offers the advantages of being fast, repeatable, less invasive, without the need for general anaesthesia, as well as the possibility of fertility preservation. In hospitals where interventional radiology expertise is available, this therapeutic option can play a pivotal role in managing PPH.

PATHOGENESIS

While uterine atony is the most common cause of PPH, accounting for 75% of cases,[4] these cases usually respond to medical therapies, such as the administration of uterotonic drugs. Placenta abnormalities, such as placenta praevia, accreta or percreta, and retained products of gestation, prohibit effective uterine contractions. UAE is more likely to be required in these cases. Lacerations of the genital tract during vaginal delivery or Caesarean section are other indications for pelvic embolisation.[5] They commonly appear as contrast extravasation or pseudoaneurysm at uterine, vaginal and internal pudendal arteries on angiograms.

VASCULAR ANATOMY

Pelvic arteries have considerable individual variations. Proper identification of uterine artery anatomy and bleeding sources, and accurate interpretation of the angiographic findings such as the presence of contrast extravasation or pseudoaneurysm, are essential for a safe and effective UAE procedure.

The uterine artery arises from the anterior trunk of the internal iliac artery. It constitutes the major arterial supply to the uterus. It typically shows a U-shaped configuration, consists of a parietal segment which runs downward and medially, a transverse segment which runs medially and an ascending segment which runs along the side of the uterus. (Fig. 1) Collaterals supply from the ovarian artery, round ligament artery, internal pudendal artery and inferior mesenteric artery can also be the bleeding sources in PPH.[6] The knowledge of this anatomy is important, as we may need to check for other collateral supply if there is clinical evidence of persistent bleeding after successful embolisation of uterine arteries.

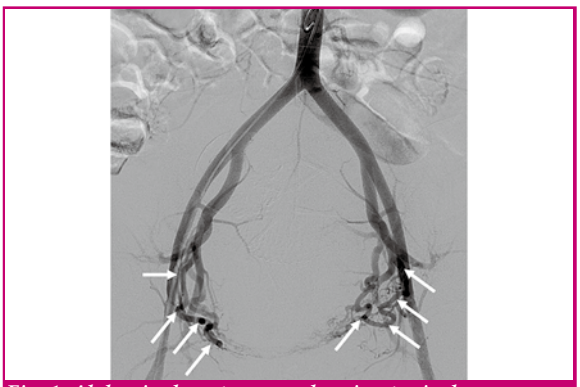


Fig. 1. Abdominal aortogram, showing typical appearance of uterine arteries (arrows).

MULTIDISCIPLINARY MANAGEMENT

Setting up a protocol for managing PPH patients improves the clinical outcomes for these patients.[7] It facilitates a standardised and coordinated approach in assessing and monitoring the patients with PPH, and timely involvement of the multi-disciplinary team. Delayed management is a known major factor contributing to the adverse clinical outcomes of PPH patients.[8] A good example of PPH protocol is the American College of Obstetricians and Gynecologists' obstetric haemorrhage checklist.[9]

At our institution, a dedicated multi-disciplinary team involving senior obstetricians, anaesthesiologists, experienced interventional radiologists and radiographers, as well as specialised scrub nurses is established. Early involvement of the interventional radiologists is crucial in decision-making and case management. For patients with placental abnormalities, our interventional radiology team would be informed early. As a precautionary measure, we will insert an arterial sheath for the patient in the operation theatre before her delivery. This would save time for the subsequent emergency UAE if PPH occurs. In our experience, the UAE procedure can be completed within 30 minutes in the majority of patients. The clinical outcomes of these patients managed by our multi-disciplinary team are promising, without the need for subsequent hysterectomy in the past 10 years.

TECHNIQUES

Firstly, we secure a femoral arterial vascular access by the Seldinger technique, with a vascular sheath

applied. Ultrasound guidance is particularly useful in haemodynamically unstable patients with small arteries. Femoral sheath placement can be done before delivery in selected patients such as those with known placenta accreta, for whom UAE is expected. When two interventional radiologists are available, vascular accesses from bilateral femoral arteries can achieve faster embolisation with reduced radiation doses.

Secondly, a Cobra catheter or Roberts uterine catheter is used to cannulate the contralateral and ipsilateral internal iliac arteries. A contralateral oblique view of around 30 degrees can be very useful in assisting the cannulation of the internal iliac arteries.[10] An internal iliac angiogram is then performed at this stage to identify the vascular anatomy, looking for any hypertrophied vessels, extravasation, pseudoaneurysms, as well as bleeding from other arteries such as the internal pudendal artery. Further selective cannulation of the uterine artery is performed. Uterine artery can usually be cannulated without the need of a microcatheter as the vessel is hypertrophied in the pregnant state.

Finally, uterine artery embolisation using absorbale gelatin sponge (Gelfoam) is performed. It is usually mixed with diluted water-soluble contrast to form a slurry for embolisation. The embolisation endpoint is complete stasis of contrast on angiograms. Gelfoam carries the advantage of achieving temporary arterial occlusion with recanalisation of target arteries within weeks. Studies reported that women underwent UAE with gelfoam could have successful conception afterwards.[11] It has also been reported that there are no significant differences in fertility between women with PPH who underwent previous UAE and those who did not.[12] In selected patients, other materials such as N-butyl cyanoacrylate (NBCA) could be used. NBCA would be useful for haemodynamically unstable patients who failed Gelfoam embolisation, or for patients with presence of contrast extravasation and pseudoaneurysm.

Bilateral embolisation would be performed in all patients. It would be conducted in patients with PPH even when the active bleeding site could not be identified on angiogram. In some patients with clinical emergency and yet selective cannulation of the uterine arteries deemed difficult, embolisation at the anterior trunk of internal iliac artery would be performed. Most importantly, there should not be any reflux of embolisation materials into the external iliac artery. An example of successful UAE is shown (Fig. 2).

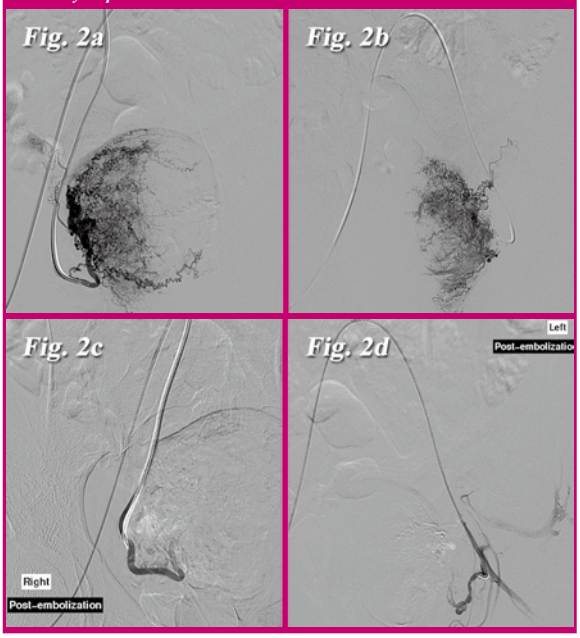
POTENTIAL COMPLICATIONS

The complication rate of UAE is low. Major complications such as non-target embolisation leading to lower limb ischaemia, and dissection of the internal iliac artery, should be extremely rare given good technique by experienced interventionist. Minor complications rates range from 3-5% post-embolisation syndromes (pain, nausea, transient fever, and leukocytosis), altered menstruations (heavier menses, lighter menses and dysmenorrhoea), transient buttock ischaemia, and puncture site haematoma.[13]

SUMMARY

Uterine artery embolisation is a safe and effective procedure for managing patients with postpartum haemorrhage. Setting up a protocol with involvement of a multi-disciplinary team improves the clinical outcomes. Good knowledge of the pelvic arterial anatomy and skilful embolisation techniques are the keys to success.

Fig. 2. A 36 year-old lady presented with PPH. Pre-embolisation angiograms with selective cannulation of (a) right and (b) left uterine arteries, showing hypertrophied and tortuous vessels without active extravasation. Post-embolisation angiograms at (c) right and (d) left uterine arteries, showing stasis of blood flow, which indicates a successful procedure.



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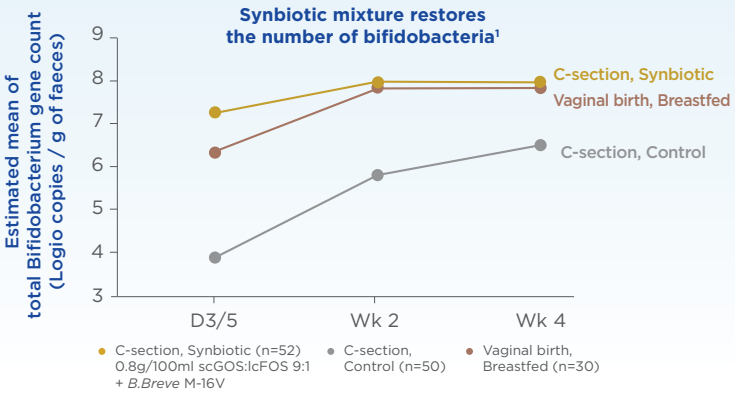

Study design[1]

Multi-country, exploratory, randomised, double-blind, controlled study. 16 weeks intervention + 6 wks follow-up. 183 infants were randomly assigned to 1 of 3 formula groups: - Control Group (n=50) - 0.8g/100ml scGOS/lcFOS 9:1 + B. Breve M-16V (n=52) - Vaginal delivery + breastfeeding [Reference group] (n=30) ▲C-section delivered infants

References: 1. Chin Chua M, et al. JPGN, 2017; 65:102-6.

Important Notice:

Breast-feeding is the best form of nutrition for babies and provides many benefits to babies and mothers. It is important that, in preparation for and during breast-feeding, pregnant and lactating women eat a healthy, balanced diet. Combined breast and bottle-feeding in the first weeks of life may reduce the supply of their own breast-milk, and reversing the decision not to breast-feed is difficult. Always consult healthcare professional for advice about feeding baby. If infant formula is used, mothers / care givers should follow manufacturer's instructions for use carefully– failure to follow the instructions may make baby ill. The social and financial implications of using infant formula should be considered. Improper use of an infant formula or inappropriate foods or feeding methods may present a health hazard.

Dermatology Quiz

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Specialist in Dermatology and Venereology

Fig.1: Dystrophic Nails

This 64-year-old gentleman with good past health attended our clinic because of deformity of his nails. He claimed the situation had lasted for years and was static. There were not many symptoms except occasional pain. Physical examination revealed curve-like dystrophy of the nails (Fig. 1).

Questions

1. What is the diagnosis for this gentleman?
2. What is the cause of the skin lesion?
3. How do you manage this condition?

(See P.36 for answers)

Peripartum Hysterectomy for Massive Postpartum Haemorrhage

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INTRODUCTION

Peripartum hysterectomy (PH) is defined as hysterectomy or Caesarean hysterectomy performed within 24 hours of a delivery. It was first proposed in the 1700s. In 1869, the gravid uterus was for the first time amputated from a living woman by Horatio Storer[1] and the first premeditated PH with both infant and mother surviving was performed by Eduardo Porro in 1876[2].

In present times, PH is generally performed to save the life of the mother in cases of major obstetric haemorrhage particularly when all conservative methods have failed.

PH is best avoided as it is associated with substantial maternal morbidity and mortality and results in infertility. Morbidity ranges from 30-44%[3] and mortality rate can be as high as 4%[4]. Multiple medications, uterine balloon tamponade, haemostatic compression sutures, uterine artery embolisation and vessel ligations are methods commonly used to arrest the rapid bleeding during massive obstetric haemorrhage hence reducing the risks of needing a peripartum hysterectomy. However, PH is still required in certain cases in order to preserve the life of the mother.

In this review article, we will review the incidence, causes and technique of performing a peripartum hysterectomy as well as identifying ways to avert the need for a peripartum hysterectomy.

INCIDENCE

Incidence of PH varies from country to country and is rising[5]. The UK Obstetric surveillance system (UIOSS) study found its incidence to be 0.41/1,000 births[6]. This is comparable to many countries worldwide such as Denmark (0.24/1,000)[7]; Holland (0.33/1,000) (4); Canada (0.35/1,000)[8] and Ireland (0.28/1,000)[9]. However, the incidence is found to be higher in the US (0.82/1,000)[5] and Australia (0.85/1,000)[10] while data from Hong Kong suggest a figure between (0.25-0.62/1,000)[11,12].

CAUSES AND RISK FACTORS LEADING TO A PERIPARTUM HYSTERECTOMY

The vast majority of PH cases were associated with massive obstetric haemorrhage[13]. Leading risk factors for massive obstetric haemorrhage leading to PH include placenta praevia, morbid adherent placenta and uterine atony. They represented over 70% of all indications for needing a PH[5] with morbid adherent placenta being the leading cause.

In recent times, changing characteristics of the delivering population and obstetrics in both Hong Kong and worldwide have driven up the prevalence of these known risk factors leading to a PH. For example, there is a rising prevalence of pregnant women with advanced maternal age, multiple gestations, hypertensive disease of pregnancy, increased rate of Caesarean Section and rising induction rates, which are all risk factors of uterine atony and contribute an overall 130% increase in associated hysterectomies in a 14 years span[5].

While a rising number of caesarean sections is certainly associated with the rising incidence of placenta praevia and morbid adherent placenta, there is also an overall 23% increase in associated hysterectomies caused by these factors[5].

Uterine rupture and uterine laceration during a Caesarean section are other known risk factors. These are mostly contributed by a history of Caesarean section and its constantly rising rate also contributes to the rise in associated PH[14].

Other indications of PH may include underlying haematological conditions, leiomyoma, high-grade cervical intraepithelial neoplasm, early invasive cervical cancer or uterine infection that failed to respond to postpartum antibiotic therapy[15].

PREVENTION

Pre-delivery antenatal planning is pivotal in the prevention of a peripartum hysterectomy. Unnecessary Caesarean sections should be avoided as morbid adherent placenta and uterine ruptures are nearly always associated with a previous Caesarean section.

Optimal management and prevention require a coordinated approach. A multidisciplinary team involving obstetricians, anaesthetists, radiologists, haematologists, blood bank, midwifery staff and other supporting services may be required. Occasionally urologists and / or gynaeoncologists may also be needed especially in cases of placenta percreta. It is well documented that a lack of antenatal care, insufficiency of resources, doctors' delay, inadequate transfer practices and poor planning contribute to higher incidences of peripartum hysterectomy[4].

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Source: 1. IMS 2010 Cord Blood Bank Market Research in Hong Kong (with Private O&G physicians) 2. Ipsos Healthcare 2018 Cord Blood Bank Survey #Among private local cord blood banks

Provision and prompt transfusion of red blood cells and other blood products via haematologists and blood bank is vital. Lack of blood products may lead to irreversible disseminated intravascular coagulopathy, which can be life-threatening.

Pharmacological agents such as misoprostol, oxytocin, duratocin, ergometrine, carboprosts, Novo – 7 shall be given promptly.

Failure to control the bleeding with medical measures warrants immediate surgical management in the operating theatre if the patient is not in one already. An ultrasound-guided insertion of the uterine tamponade balloon may reduce bleeding up to 70-100% of cases and avoid 80-85% of the need for a laparotomy[16]. Laparotomy and uterine compression sutures such as B Lynch or modified sutures may be attempted with success rates of over 60%[12] while uterine artery or iliac artery ligation could arrest 62% of haemorrhages and avoid PH[17].

Inserting balloon catheters into bilateral pelvic arteries before the operation and subsequent balloon inflation to achieve temporary curtailment of the uterine blood supply have been reported but effects are mixed[18-21].

Nonetheless, it is advisable for every obstetric unit to have protocols in place regarding the management of massive obstetric haemorrhage. Standard of antenatal care should be established. Post-graduate training is also important particularly when 59.3% of cases of PH were found to have substandard factors within the care team.[22]

TECHNIQUES OF A PERIPARTUM HYSTERECTOMY

Personnel Performing the Procedure

Peripartum hystectomy should be carried out by a senior obstetrician. Under current climate, the majority of the obstetric units are staffed with in-house specialists. However, if such built-in personnel is not possible, a senior obstetrician must be sought immediately.

Timing of the Procedure

Hysterectomy is often carried out too late, by which time the patient may be coagulopathic, hence increasing the morbidity of the procedure. In certain situations such as placenta percreta, irreparable ruptured uterus, or when conservative measures are unsuccessful, the recommendation from international college guidelines is to proceed straight to hysterectomy. This option should also be considered depending on the patient's fertility wish.[23,24] Threshold is generally much lower when the patient has confirmed to have completed her family.

In some situations, a patient may prefer a planned Caesarean hysterectomy. The American College of Obstetricians and Gynecologists (ACOG) recommends planned Caesarean hysterectomy in the 34th week of gestation[24] as all perinatal mortalities reported were below the 32nd week of gestation. In an ideal world, a Caesarean hysterectomy may be planned in the late third trimester but there is an increased risk of needing an emergency procedures during this delayed period. Emergency procedures are associated with increased morbidity to the pregnant mother and hence recommendation for a planned Caesarean hysterectomy is at 34 weeks.

Technique of the Procedure

Usually a standard subtotal abdominal hysterectomy (STAH) is sufficient to control the bleeding. If a uterine tear or uterine rupture extends into the cervix or there is lower uterine segment bleeding after a major placenta praevia, the cervix will also be need to be removed by total abdominal hysterectomy[23]. A STAH is associated with a shorter procedure time, less urological injuries and less blood transfusion; however, these differences have not been found to be statistically significant[25,26,27]. During the procedure, exteriorising the uterus may be of benefit. Exteriorisation and upward traction causes uterine artery constriction, which in turn may help to diminish blood loss.

If a PH is performed for a high-grade placenta praevia or morbid adherent placenta, pre-operative assessment is key and may reduce mortality and mortality. Pre-operative ultrasound or MRI confirming the depth of invasion of the placenta should be performed and allows mapping of the placenta so that one can avoid cutting into the placenta during entry into the uterus. Pre-operative discussion with the patient on whether or not to leave the placenta in situ in order to prevent life-threatening bleeding is an option, and this option becomes less difficult if the patient has completed her family.

In general, if a morbid adherent placenta is confirmed and delivery is to proceed via a Caesarean section, the less invasive measures mentioned above (such as compression sutures, uterine artery embolization etc.) should be attempted before performing a PH. In the management of patients with placenta accrete, a staged technique where the patient first undergoes a classical Caesarean section without removal of the placenta, followed by arterial embolisation then hysterectomy was found to be associated with significant reduction in operative blood loss[28].

It is advisable to undertake a classical Caesarean section via a midline incision[27] as this approach provides sufficient exposure. Classical uterine incision towards the fundus thus avoiding the previously mapped placenta may reduce the risk of bleeding. If the placental invasion is extensive as in the case of placenta percreta, separating the bladder wall from placental adhesion may result in life-threatening bleeding[29]. In the presence of placenta percreta extending towards anterior or lateral side of the uterus, some authors suggested pre-operative urethral stenting. In such situations, the presence of a urologist and / or gynaeoncologist may be helpful.

Other than the routine TAH or STAH, Selman et al[30] described a novel technique in the management of anterior placenta praevia / accrete. The technique involves exposing the posterior vaginal fornix at the Pouch of Douglas by placement of a sponge stick into the vagina. Once the cervicovaginal junction has been identified, the vagina is divided and sutured

under direct vision. The flow from different types of vaginal anastomosis interconnected or in the thickness of the cervicovaginal junction is interrupted and devascularised. The main improvement over other techniques is the blunt dissection of the bladder, moving away from the trigone level, once the uterus is completely devascularised.

Intra-operative use of Cell salvage for autologous transfusion of salvaged blood should be considered to minimise allogenic transfusion[31] as well as to reduce the amount of blood products needed to be transfused. This is particularly important in countries where blood product availability is limited.

In all PH, if haemostasis is not totally satisfactory, Fawcus et al. recommended to leave a suction drain[23]. Abdominal packing to tamponade the abdominal cavity can be considered if coagulopathy is evident after STAH or TAH. At least 5 large abdominal packs are advised when undertaking abdominal packing while it must be stressed that packing should be done only after having fully secured and ligated all major vessels[32]. If packing is used, ideally pack removal should not be attempted till full correction of haemodynamic and coagulation disorders, such correction usually takes another 48-72 hours[23, 33]. Re-laparotomy is usually required for pack removal; however, as packs are not generally adherent, re-laparotomy might be avoided by using continuous wide gauze pack and bringing the end out through the abdominal wall incision or through the vaginal vault[32].

Complications of the Procedure

On-going bleeding, coagulopathy and subsequent massive blood transfusions are the main complications of the procedure. Average blood transfusion ranges between 6-12 units[23] with occasional instances where double or triple that amount may be needed. Transfusion-related acute lung injury and postoperative bleeding may also occur precipitating the need for intensive care management post-operatively.

Injury to bowel, bladder, and/or urinary tract may also be a potential possibility especially if it involves placenta percreta.

POST-Operative MANAGEMENT

The majority of patients who underwent a peripartum hysterectomy are also likely to have suffered from massive obstetric haemorrhage. Given the amount of blood transfusions and other life-saving interventions given peri-operatively, the patient warrants intensivists' input. Further strict monitoring of fluid balance, blood transfusions and line (CVP and arterial lines) management are best undertaken in the intensive care unit. Hence unless logistically not feasible, all peripartum hysterectomies should be performed in centres with ICU facilities and all planned Caesarean hysterectomies should be performed in similar centres or transferred to one with full ICU backup.

DISCUSSION

Peripartum hysterectomies are associated with high morbidity and mortality to the patients. The incidence of such procedure has been markedly reduced, thanks to advancement in medical, surgical and radiological interventions. Rising Caesarean rates will lead to increased likelihood of adherent placenta which is the most prevalent cause of peripartum hysterectomy. As a result, we may yet see an increasing rise in the incidence of peripartum hysterectomy in the future. As obstetricians, we should avoid peripartum hysterectomy via good antenatal planning through multidisciplinary approach and we should all aim to reduce unnecessary Caesarean sections in order to preserve a healthy uterus.

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Postpartum Haemorrhage from a Research Perspective

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Postpartum haemorrhage (PPH) is one of the top five causes of maternal mortality in both high and low income countries. On average, PPH accounts for 20% of maternal deaths worldwide while 23% of maternal deaths in Southeast Asia region are caused by PPH.[1] In 2013, the incidence of massive PPH (defined by ≥ 1,500 ml blood loss within 24 hours of delivery) is 1% in Hong Kong.[2] The rates in the subsequent years have been fluctuating (unpublished). However, an upward trend of PPH has been widely reported in many countries including the U,K., the U.S.A., Australia, Netherlands, Norway, Canada and other high-resource countries.[3] Given its increasing incidence rates and severe impact on maternal lives, prevention and management of PPH should be prioritised in both clinical and research settings. Clinically, massive PPH is one of the performance indicators of obstetric service in Hong Kong. On the research side, unfortunately, in the past decade, less than 20 PPH-related publications from Hong Kong were identified on Pubmed. Little is known about the epidemiology, risk factors and responses to treatment for PPH in Hong Kong. We need more local data to support or refute international guidelines which may or may not be applicable to our population and hospital settings. The aim of this article is to give some insights into research in PPH, under the five 'W's – what, why, who, when and where?

WHAT IS PPH?

Multiple criteria for diagnosing PPH are in use globally. The World Health Organization (WHO) defines PPH as 500 ml of blood loss within 24 hours after birth and 1,000 ml for severe PPH.[4] The Royal College of Obstetricians and Gynaecologists (RCOG) endorses the following definitions - minor PPH (500 to 1,000 mL) and major PPH (>1,000 mL) which is subdivided into moderate (1,001 to 2,000 mL) or severe (>2,000 mL).[5] Across the Pacific Ocean, the American College of Obstetricians and Gynecologists defines PPH as cumulative blood loss ≥1,000 mL or blood loss accompanied by signs or symptoms of hypovolaemia within 24 hours after the birth process (including intrapartum loss) regardless of the route of delivery.[6] Without a consistent definition, it is very difficult to see the trends and to make comparisons. In Hong Kong, since 2015, a standardised documentation form for massive PPH has been incorporated into our Clinical Management System (CMS) and we adopt 1,500 ml as the cut-off point. With the same definition over the years, these data will provide strong power for studying the temporal trends, risk factors, causes and treatment profiles of our local PPH cases. An alternative method to capture PPH events from medical records is using administrative ICD coding. However, it is well known in the research field that ICD codes are either under-coded or mis-coded.[7] The data, e.g. causes or severity, cannot be well differentiated by the codes themselves.[3] Furthermore, the measurement of blood loss is often inaccurate. None of the methods (visual estimation, calibrated drapes, gravimetric technique, or even more precise ways like haemoglobin, spectrophotometry or radioactive tracer) has been shown to be superior to another. It is believed that any clinical trial in this area should focus on the impact on clinical outcomes, along with the diagnostic accuracy.[8]

WHY IS RESEARCH IN PPH IMPORTANT?

In addition to the aforementioned points, people around the world have also realised the importance of research priorities in obstetric haemorrhage. The Child Health and Nutrition Research Initiative (CHNRI) called for research questions from over 2,700 institutions in more than 160 countries, about maternal and perinatal health improvement for the upcoming decade (2015-2025). Obstetric haemorrhage (misoprostol access, type/dose/route of uterotonics, screening and detection, training and/or awareness, care quality, blood transfusions, management in the third stage) is the second priority theme after labour/delivery.[9] However, in Hong Kong, as a result of patient overload, overstretched public hospital system and staff shortage at all levels, research becomes a luxury or even a burden to the frontline medical personnel. More resources and protected research time should be reserved for medical staff with research interests. The benefits of creating a more conducive environment for research in PPH are two-fold. One is to reduce the incidence of PPH and its economical (medical expenses arising from intensive care, blood products, etc.) and clinical impact (maternal morbidity and mortality); Second is to replace any outdated, ineffective and sometimes harmful forms of care which in reality have taken up valuable resources at subconscious levels, e.g. continuous foetal heart monitoring in the second stage of labour, routine episiotomy, frequent high number of antenatal visits, etc.[10] Currently, most of our practices in PPH management come from international guidelines which are characterised by respective recommendations tailored to their particular populations. Race, body composition, sociodemographic context, environment, hospital facilities, treatment options and experience of medical staff in Hong Kong may be very different from their target groups. Local data and research are

definitely necessary to develop local guidelines which are more applicable to our population.

WHO SHOULD BE INVOLVED IN RESEARCH IN PPH?

Anyone who is interested in combating PPH and protecting maternal well-being should be involved in it. Current state of knowledge about PPH is still deficient in biology, prevention and treatment.[10] Basic scientists, statisticians, epidemiologists, medical doctors, midwives, anaesthetists, radiologists, psychologists, psychiatrists, family physicians, medical/nursing students, patients, or whoever you can name, can play a role in research.

WHEN SHOULD RESEARCH BE STARTED?

Start NOW. It's never late or early. There are a lot of unknown answers to clinical questions, and over 50 actively recruiting PPH-related clinical trials registered with ClinicalTrials.gov, e.g. tranexamic acid and different forms of uterotonic agents (misoprostol, carbetocin, ergometrine, etc.). Clinical questions come from observations, followed by hypotheses. Build your research question in the format of PICO (population, interventions, comparators, outcomes). Be creative, realistic and scientific. Most of the time, a more convincing and compelling research question will lie on plausible biological links. For example, if the research question is 'does antepartum depression increase the rate of PPH in Chinese mothers?', it is still possible to show the associations but it is difficult if not impossible to explain it biologically. The second important thing is clinical relevance. If the research findings are going to change the clinical practice, such research will carry a high impact.

WHERE SHOULD RESEARCH BE CARRIED OUT?

Academic institutions are well known to perform research studies because of the study environment, research resources and funding. But research should never be limited to academic centres or university-affiliated hospitals, which usually include a high proportion of high-risk or referral cases, leading to a biased result. In fact, well-designed research studies performed in community hospitals are of significant values as the results are more generalisable to the local population and sometimes more powerful when the patient turnover is high and the sample size is large.

FUTURE DIRECTIONS

Hong Kong is small but dense with millions of patients including women of reproductive age. Maternal and neonatal safety is the top priority for every obstetrician and midwife. The best practice is always performing evidence-based medicine. We need more local data from Hong Kong on PPH, especially at patient-level (e.g. maternal or labour risk factors, induction methods, etc.) and healthcare system-level (e.g. effectiveness and cost of training interventions for frontline medical personnel, impact of local research findings on clinical practice, etc.). Collaborating with experienced researchers and performing well-deigned studies with robust input from perinatal, epidemiologic and scientific teams will be the next step.

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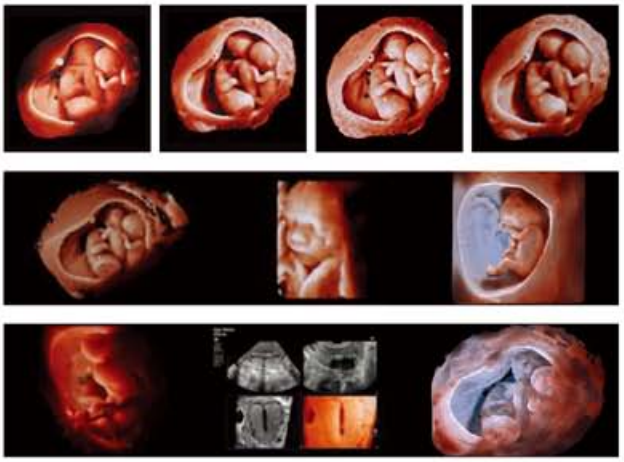

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An Update on Medical Indemnity in Hong Kong

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Medical indemnity protects and assists doctors in the events of medical incidents and complaints. In a broad sense, it is a rescue mechanism to doctors in distress, although it is usually seen as mere coverage for financial compensation and expenses locally. History taught us that claims could be devastating not only to the reputation of doctors. They also demolished one of the largest medical indemnity organisation in Australia in 2001[1]. Doctors might learn from facts and reality, instead of burying ourselves in good feelings or beautiful pictures, if we do not want to repeat history in a hard way.

Public doctors employed by the Hospital Authority or Department of Health are generally supported financially on clinical negligence claims. However, the Hospital Authority or Department of Health may not compensate nor assist doctors in medico-legal proceedings. Recently, the Hospital Authority arranged corporate-based medical indemnity insurance for employed doctors. The author understands that, in the event of litigation, doctors will be supported legally as if they have independent coverage. However, a single employee might still be concerned about the possible need to be grossly aligned with an employer organisation in a difficult situation. Public doctors, notwithstanding the coverage, could purchase additional medical indemnity insurance at their arrangement.

A self-employed doctor in the private sector himself is the sole driver to shop for the right coverage and limits for himself and to match the preferences of visiting hospitals. Traditionally, the Medical Protection Society (MPS) pictures a utopia of infinite coverage in most countries by declaring no annual compensation limit per subscribed doctor. Recently, MPS imposed an upper annual limit to an obstetrician. If such declared limit is exceeded in compensations, doctors would have to pay the difference out-of-pocket. It is unrealistic to hope that such treatment to obstetricians is a once-off arrangement while other doctors stay immune forever.

Acturists of indemnity providers consider an occurrence-based policy outdated and thorny, as it is nearly impossible to estimate claim conditions sometimes after a doctor retires at 65 or 70 years old, and do it at the time when the same doctor starts to practise when he is only 25. In an occurrence-based indemnity model, subscribed doctors show little interest in adverse event reporting as they may expose themselves to potential discretionary sanction by a provider. Thus, occurrence-based indemnity providers do not even have accurate statistics to measure and manage risks. Unluckily, the indemnity provider might then have to manage its risks with the removal of some doctors from coverage.

Claims-made policies, in contrary, are favoured by indemnity providers for its adjustable policy limits and coverage for incidents and claims strictly within the policy period. Subscribers are also required to submit case reports when potential claims occur. Hence, indemnity providers could audit and calculate risk for individual doctors. A provider may adjust premium, or discuss the scope of practice and therefore risk with an affected doctor. Paradoxically, this arrangement may allow the insurer to continue covering a doctor, instead of exiling him. Claims-made policies could also offer a more reasonable and differential premium among subscribers, through appropriate mechanisms. The user input may be provided with collective representation by professional bodies, as well as transparency in final costing. It is worthy to note that doctors under claims-made policies are required to subscribe for an additional tail-cover plan following their retirement based on risk records. Many indemnity companies are happy to offer reasonable tail-cover schemes for doctors[2,3]. Under some arrangements, senior doctors who retire after subscription for a reasonable duration might enjoy free tail coverage.

Besides individual indemnity insurance, private group practices also need to arrange practice-based indemnity insurance to protect affiliated employees (nurses, clinic assistants, administrators) in the organisations. Doctors in a group practice (starting with two partners) might face formal challenges for compensation to the group and its employees. Even when each doctor is individually covered, the responsibility of the clinic employee is often not covered by an individual doctor indemnity scheme. This type of indemnity coverage is usually not very expensive, and they are predominantly claim-made based.

The medical services inflate annually at around 9% in Hong Kong and some Asian countries[4]. Until today, a reform of the tort law, Cap.314 Occupier Liability Ordinance to cap the claims on public liability and medical negligence still has not been in place in Hong Kong[5,6]. On top, law interpretation may change prospectively as demonstrated in the Montgomery v Lanarkshire Health Board (2015) case[7]. These policy and economic influences make it hard to predict compensation, in both occurrence and claims-made scheme. Notably, the claims-made approach is more equipped towards the vast future. Finally, it may

be time for our fraternity to consider the role of asset protection in an increasingly litigious society. A family trust, abiding by the Trustee Ordinance (Cap.29) and the Perpetuities and Accumulations Ordinance (Cap.257), is a recognised vehicle to manage assets[8,9].

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Medical Diary of July

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2 ★ HKMA-HKS&H CME Programme 2018 -2019 (Live) –Photoprotection and Skin Cancers ★ FMSHK Officers' Meeting ★ HKMA Council Meeting	3 ★ Certificate Course in Clinical Cytogenetics and Genetics 2019	4 ★ HKMA Hong Kong East Community Network - Bowen Therapy: Clinical Application in Occupational Therapy ★ HKMA Kowloon East Community Network & UCH & FP (Cert Course for GP 2019): Approach to Carcinoma of Breast Cancer ★ Certificate Course in Allergy 2019	5 ★ Certificate Course on Essential Healthcare Mediation 2019	6
7 ★ Symposium on Atrial Fibrillation Management	8	9 ★ HKMA Kowloon West Community Network – Update in the Management of Idiopathic Pulmonary Fibrosis	10 ★ The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed ★ HKMA Central, Western & Southern Community Network – Steering Towards Control-Driven Management Tactics for Better Asthma Control ★ Certificate Course in Clinical Cytogenetics and Genetics 2019	11 ★ HKMA New Territories West Community Network – Updates on Antiviral Treatment for Influenza ★ Certificate Course in Allergy 2019	12 ★ HKMA Shatin Community Network - Updated Guidelines and Role of ONS for Type II Diabetes ★ HKMA and Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 3) - Strange Behavior or Treatable Psychiatric Symptoms II ★ Certificate Course on Essential Healthcare Mediation 2019	13
14	15 ★ Certificate Course on Care for Advanced Diseases	16 ★ HKMA Yau Tsim Mong Community Network - Lecture Series on Thyroid Disease (Session 1) – Nonsurgical Management of CA Thyroid ★ Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019	17 ★ Certificate Course in Clinical Cytogenetics and Genetics 2019	18 ★ HKMA Hong Kong East Community Network - Managing Injury-On-Duty (IOD) in General Practice ★ Certificate Course in Allergy 2019	19 ★ Certificate Course on Essential Healthcare Mediation 2019	20
21 ★ Annual Charity Concert	22 ★ Certificate Course on Care for Advanced Diseases	23 ★ HKMA Kowloon West Community Network – Improving Dyslipidaemia Management: An Update on International Guideline and More ★ Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019	24 ★ HKMA and Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 4) - Disability Assessment and Other Medical Legal Issues ★ HKMA Central, Western & Southern Community Network – Common Surgical Diseases: From Primary Care to Surgery ★ Certificate Course in Clinical Cytogenetics and Genetics 2019	25 ★ HKMA Kowloon East Community Network – The Changing Landscape of Personalized Treatment of Metastatic Non-Small ★ HKMA New Territories West Community Network – Biomechanical Management of Common Podiatric Dermatological Problems ★ Certificate Course in Allergy 2019 ★ HKFMS Foundation Meeting ★ FMSHK Executive Committee Meeting	26 ★ HKMA Yau Tsim Mong Community Network - Lecture Series on Thyroid Disease (Session 2) - Management of Thyroid Nodule - An Overview	27
28	29 ★ Certificate Course on Care for Advanced Diseases	30 ★ Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019	31 ★ Certificate Course in Clinical Cytogenetics and Genetics 2019			

Date / Time	Function	Enquiry / Remarks
2 TUE 1:00 PM	**HKMA-HKS&H CME Programme 2018 -2019 (Live) –Photoprotection and Skin Cancers** Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr. KUNG Ka Yee; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Dept Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
3 WED 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
4 THU 1:00 PM	**HKMA Hong Kong East Community Network - Bowen Therapy: Clinical Application in Occupational Therapy** Organiser: HKMA Hong Kong East Community Network; Speaker: Mr. David CHIN; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network & UCH & FP (Cert Course for GP 2019): Approach to Carcinoma of Breast Cancer** Organiser: HKMA Kowloon City Community Network; Speaker: Dr. LAW Siu King; Venue: Lecture Theatre, G/F, Block K, United Christian Hospital	Ms. Polly TAI Tel: 3513 3430 1 CME Point
7:00 PM	**Certificate Course in Allergy 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
5 FRI 7:00 PM	**Certificate Course on Essential Healthcare Mediation 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
7 SUN 1:00 PM	**Symposium on Atrial Fibrillation Management** Organiser: Hong Kong Medical Association & The Hospital Authority; Speaker: Dr. LAI Wai Keung, Steve, Dr. CHEUNG Chun Ming, Prof. SIU Chung Wah, David, Dr. CHAN Kwok Keung & Dr. CHEUNG Shing Him, Gary; Venue: Lecture Theatre, G/F, Centre for Health Protection, 147C Argyle Street, Kowloon	HKMA CME Dept. Tel: 2527 8285 3 CME Point
9 TUE 1:00 PM	**HKMA Kowloon West Community Network – Update in the Management of Idiopathic Pulmonary Fibrosis** Organiser: HKMA Kowloon West Community Network; Speaker: Dr. CHAN Ka Wing, Joseph; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr CHAN Kwong Yau; Speaker(s): Dr HO Wing Kiu, Joanna; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061 1.5 points College of Surgeons of Hong Kong
1:00 PM	**HKMA Central, Western & Southern Community Network – Steering Towards Control-Driven Management Tactics for Better Asthma Control** Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. CHIU Chung Ming, MH; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
11 THU 1:00 PM	**HKMA New Territories West Community Network – Updates on Antiviral Treatment for Influenza** Organiser: HKMA New Territories West Community Network; Speaker: Dr. YEUNG Koon Sing; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, Yuen Long	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Allergy 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
12 FRI 1:00 PM	**HKMA Shatin Community Network - Updated Guidelines and Role of ONS for Type II Diabetes** Organiser: HKMA Shatin Community Network; Speaker: Dr. YUEN Mae Ann, Michele; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA and Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 3) - Strange Behavior or Treatable Psychiatric Symptoms II** Organiser: Hong Kong Medical Association; Hong Kong Society of Biological Psychiatry; Speaker: Dr. YEUNG Ming Hong, Dr. TSANG Fan Kwong & Prof. TANG Siu Wa; Venue: Tang Room, 3/FL, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 2 CME Point
7:00 PM	**Certificate Course on Essential Healthcare Mediation 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
15 MON 7:00 PM	**Certificate Course on Care for Advanced Diseases** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
16 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Lecture Series on Thyroid Disease (Session 1) – Nonsurgical Management of CA Thyroid** Organiser: HKMA Yau Tsim Mong Community Network; Speaker: Dr. CHOW Sin Ming; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898

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18 THU 1:00 PM	**HKMA Hong Kong East Community Network - Managing Injury-On-Duty (IOD) in General Practice** Organiser: HKMA Hong Kong East Community Network; Speaker: Dr. WONG Man Sze, Marcus; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Allergy 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
19 FRI 7:00 PM	**Certificate Course on Essential Healthcare Mediation 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
21 SUN 8:00 PM	**Annual Charity Concert** Organiser: The Hong Kong Medical Association & The Hong Kong Arthritis & Rheumatism Foundation; Venue: Auditorium, Kwai Tsing Theatre, 12 Hing Ning Road, Kwai Chung, N.T.,	Miss Sandy WONG Tel: 2527 8285
22 MON 7:00 PM	**Certificate Course on Care for Advanced Diseases** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
23 TUE 1:00 PM	**HKMA Kowloon West Community Network – Improving Dyslipidaemia Management: An Update on International Guideline and More** Organiser: HKMA Kowloon West Community Network; Speaker: Dr. CHEUNG Shing Him, Gary; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
24 WED 1:00 PM	**HKMA and Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 4) - Disability Assessment and Other Medical Legal Issues** Organiser: Hong Kong Medical Association; Hong Kong Society of Biological Psychiatry; Speaker: Dr. WONG Ting Chi, Dr. CHEUNG Hung Kin & Prof. TANG Siu Wa; Venue: Tang Room, 3/FL, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 2 CME Point
1:00 PM	**HKMA Central, Western & Southern Community Network – Common Surgical Diseases: From Primary Care to Surgery** Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. TSE Tak Yin, Cyrus; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
25 THU 1:00 PM	**HKMA Kowloon East Community Network – The Changing Landscape of Personalized Treatment of Metastatic Non-Small** Organiser: HKMA Kowloon East Community Network; Speaker: Dr. SZE Chun Kin, Henry; Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network – Biomechanical Management of Common Podiatric Dermatological Problems** Organiser: HKMA New Territories West Community Network; Speaker: Ms. CHAN To On; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Allergy 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
26 FRI 1:00 PM	**HKMA Yau Tsim Mong Community Network - Lecture Series on Thyroid Disease (Session 2) - Management of Thyroid Nodule - An Overview** Organiser: HKMA Yau Tsim Mong Community Network; Speaker: Dr. KAN Mei Yee, Daisy; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
29 MON 7:00 PM	**Certificate Course on Care for Advanced Diseases** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
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Answers to Dermatology Quiz

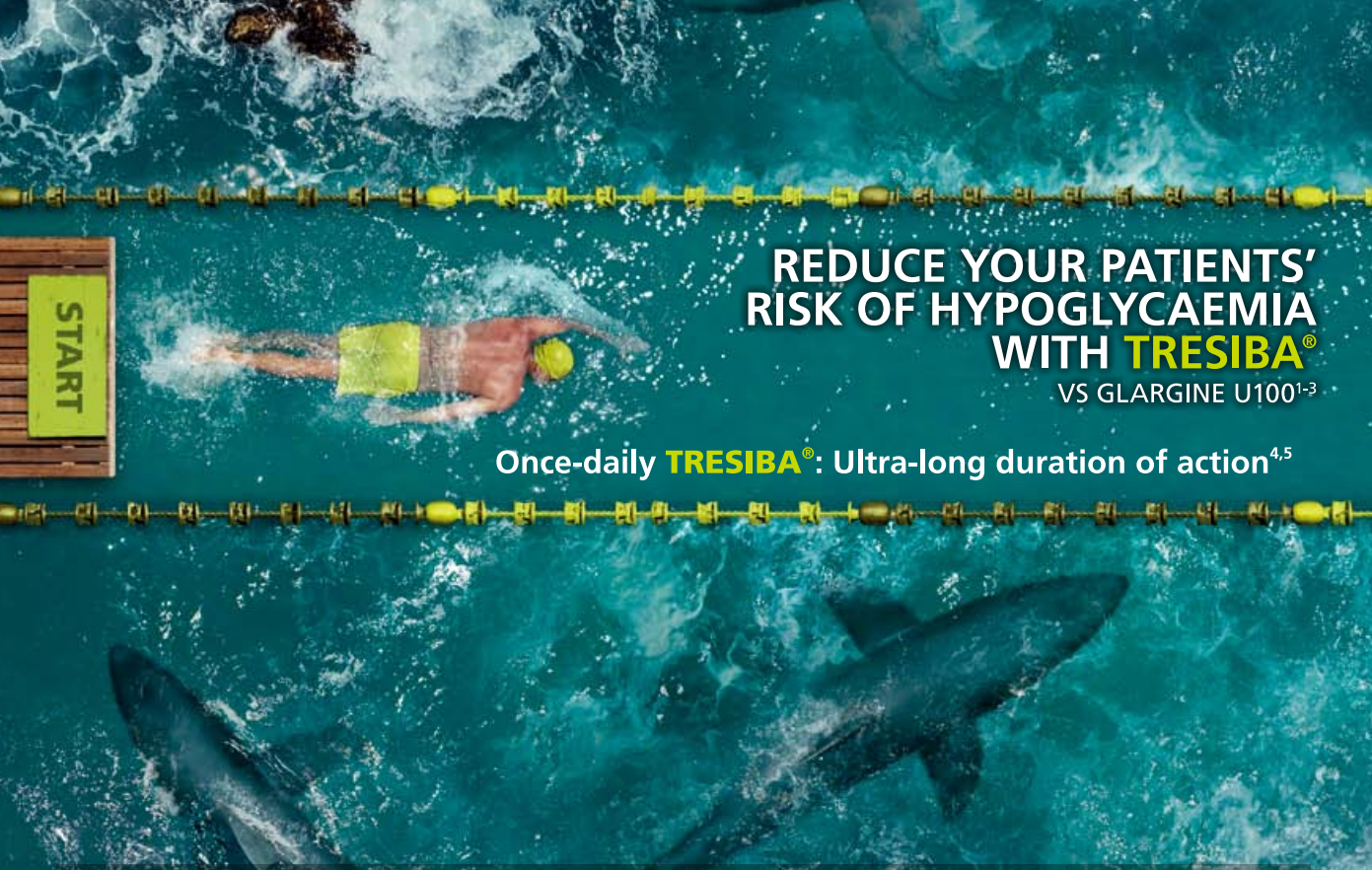
Answers:

1. Pincer Nail
   The diagnosis for this gentleman is pincer nails. The diagnosis is often made clinically. It is also called "Omega Nails". The lateral edges of the nail plate curve inwards to form an omega shape.

2. The pathogenesis of pincer nail is unknown. It is probably due to enlargement of the base of the distal phalanx thus producing an over-curvature along its long axis. Some precipitating factors including unfit shoes; trauma; tumours of nail apparatus like exostosis; myxoid pseudocyst; degenerative osteoarthritis of distal interphalangeal joints; psoriasis; onychomycosis; renal failure and medications such as epidermal growth factor receptor(EGFR) inhibitors.

3. The precipitating causes should be avoided such as unfit shoes and trauma to nails. Onychomycosis should be investigated and treated accordingly. Imaging studies such as X-rays or MRI can be used to rule out underlying tumours. A physical nail brace may be applied to correct or reduce the nail plate curvature. Surgical treatment including nail avulsion, total or partial excision of nail bed, phenol matrixectomy and so on may be needed in severe cases.

Dr Chi-keung KWAN
MBBS(HK), FRCP(Lond, Glasg), FHKCP, FHKAM(Med), Dip Derm (Glasg), PDipID (HK)
Specialist in Dermatology and Venereology



REDUCE YOUR PATIENTS' RISK OF HYPOGLYCAEMIA WITH TRESIBA®

VS GLARGINE U100[1-3]

Once-daily TRESIBA®: Ultra-long duration of action[4,5]

Tresiba® OD* VS Glargine U100 OD*

* Plus additional antidiabetic treatments in accordance with standard of care.

DEVOTE Trial[1]

In **7,637** patients with type 2 diabetes at high risk of CV events[1]

At baseline: mean age was 65 years, diabetes duration was 16.4 years, HbA_{1c} was 8.4%, and 83.9% were on insulin therapy[1]

Severe hypoglycaemia — 40% significant rate reduction (p<0.001) — -40%

Nocturnal severe hypoglycaemia — 53% significant rate reduction (p<0.001) — -53%

Abbreviated prescribing information
Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch®). Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device contains 300 units of insulin degludec in 3 mL solution. **Indications:** Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. **Posology and administration:** Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL, a dose of 1–80 units per injection, in steps of 1 unit, can be administered. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units. Transferring from other insulins: in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component; in type 1 diabetes the same applies apart from where transferring from twice-daily basal insulin or patients with an HbA1c <8.0%, the Tresiba® dose needs to be determined on an individual basis with a dose reduction considered. Doses and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus, when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia. Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine®. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups with other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. **Pregnancy and lactation:** There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. **Undesirable effects:** Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment.

References: **1.** Marso SP, McGuire DK, Zinman B, et al. for the DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine 2017; 377:723–732. **2.** Wysham C, Bhargava A, Chaykin L, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA 2017; 318(1):45–56. **3.** Lane W, Bailey TS, Gerety G, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017; 318(1):33–44. **4.** Tresiba® Packing Insert. **5.** Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharmaceutical Research 2012;29(8):2104-14

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Further information is avaliable from
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WITH PROMISING SAFETY PROFILE
PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT[1]

Harnal OCAS®
tamsulosin

YOUR 1ST STEP FOR MALE LUTS+ PATIENTS
WITH PROMISING SAFETY PROFILE#
PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT[2]

A *FRESH* STEP IN LUTS+ MANAGEMENT

*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

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