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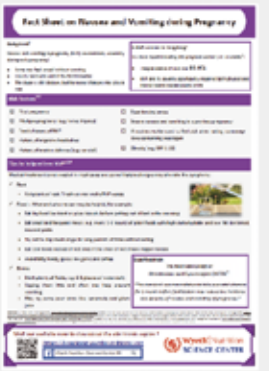
FACT SHEET ON NAUSEA AND VOMITING DURING PREGNANCY (NVP)

In a local report including 396 pregnant women (10-14 weeks), the prevalence of NVP was 90.9%! [1] Check out this fact sheet covering risk factors and tips to help relieve NVP.

Examples of risk factors:[2-4]

- First pregnancy
- Multiple pregnancy (e.g. twins, triplets)
- Family history of NVP
- History of migraine headaches
- Experiencing stress
- Obesity (e.g. BMI ≥ 25)



- Both English and Chinese version available for download
- For your reference and patient education

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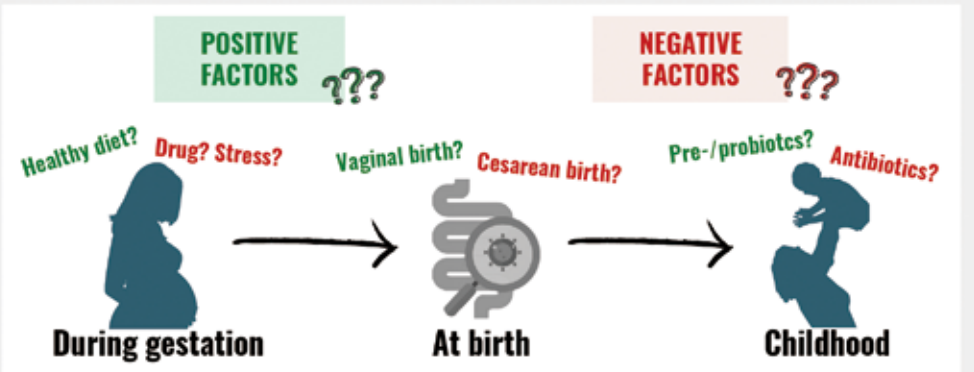
Reference: 1. Chan OK et al. Aust N Z J Obstet Gynaecol. 2010;50(6):512- 518. 2. National Health Service (NHS). Vomiting and morning sickness. https://www.nhs.uk/pregnancy/related- conditions/common- symptoms/vomiting- and- morning- sickness/. Accessed on 04 Jan 2021. 3. American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin. Number 189. 2018. 4. Centre for Health Protection. Body mass index chart. https://www.chp.gov.hk/en/resources/e_health_topics/pdfwaw_11012.html. Accessed on 05 Jan 2021.

GUT MICROBIOTA AND CHILD HEALTH INFOGRAPHIC

An overview of potential factors influencing child gut microbiota and health from gestation to childhood.



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The Cover Shot

'Light and Hope'

This photograph was taken at Yellowknife, Canada.

After three connecting flights totalling 15 hours of flight time and two long cold (-30 degrees Celcius) unsuccessful nights of aurora hunting, my aurora trip looked all doom and gloom. Suddenly, the aurora burst right above our heads at 2 am of our final night. This photograph was the first decent picture I took during this trip.

I remember after taking this photo, my fingers were pretty frozen, the camera was wrapped with heat pads, and the battery was dying by the minute. A total of six camera batteries were used, and due to the cold weather, the batteries were left with half its capacity after the trip.

By the end of the night (4 am), we shared a simple hot chocolate. It may not be the best chocolate ever, but it was definitely the best hot chocolate I had ever tasted. Simple things can sometimes be extremely gratifying at the right moment.

This photo will always remind me that our goals can be achieved with will, perseverance, and sacrifice and good things will come. With light there's hope.

Dr Menelik MH LEE
Specialist in Obstetrics and Gynaecology

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Update in Obstetrics

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In Hong Kong, the total number of births declined from 61,290 in 2014 to 53,168 in 2019.[1] Compared to the first 11 months of 2019, there was a further 17% decline in 2020.[1] Mr CK Law, Secretary for Labour and Welfare, estimated the decline would continue this year because of the COVID-19 pandemic and the economic downturn.[1] In this March issue, Dr MW Lui and Dr Raymond Li summarise the effects of COVID-19 on human reproduction and pregnancy as well as the impact on clinical services; they also outline the priorities for assisted reproduction in the current COVID-19 situation.

Pregnant women aged 35 or above is increasingly common because of late childbearing, and they are considered high-risk pregnancies. It is a usual practice to offer these women non-invasive prenatal testing with cell-free foetal DNA to screen for Down's syndrome and other aneuploidies. In addition, recent AIUM guidelines recommend detailed diagnostic ultrasound examination of foetal cardiac, brain, facial, and other structures.[2] In this March issue, I myself have contributed an article on new advances in morphology scan: from routine mid-trimester to beyond.

Knowledge of genetics and genomics has increased rapidly recently. Obstetricians and gynaecologists, and other medical professionals have increasingly incorporated genetics and genetic testing into clinical practice. In this March issue, Dr WC Leung and Dr WF Ng show us how to adopt a multi-disciplinary approach, including genetic testing, to investigate an abnormal foetus.

Two new programmes were introduced by the Hospital Authority and the Department of Health last year, namely antepartum antiviral therapy for hepatitis B carriers with high viral load, and antepartum pertussis vaccination. The former programme aims to align with the World Health Organization's initiative to eliminate viral hepatitis as a public health threat by 2030. The aim of the latter programme is to protect the newborns by giving antepartum pertussis vaccine to their mothers. In this March issue, Dr KW Cheung enlightens us on the former programme, and Prof WH Tam on the latter programme.

Traditionally, oxytocin with or without ergometrine has been used to prevent postpartum haemorrhage. Carbetocin, a newer synthetic analogue of oxytocin, can produce sustained uterine contractions within two minutes after injection. The question is under what situations carbetocin is more effective than traditional medications in reducing blood loss. Dr Baron Tse and Dr Florrie Yu review the current evidence, and provide an update on the use of oxytocic agents to manage postpartum haemorrhage.

Ideally, a medical consultation includes a face-to-face consultation, but the latter poses a potential risk of COVID-19 transmission. The Centre for Disease Control and Prevention recently suggests offering telemedicine which can provide the health care the patients need while practicing social distancing in the midst of COVID-19 pandemic.[3] In this March issue, Dr Kenneth Tsang answers some important questions related to telemedicine.

I would like to express my sincere thanks to my colleagues who have contributed to this March issue by sharing their expertise and experience despite their busy clinical schedule in the midst of COVID pandemic. I would also like to thank the great support from the Editorial Board.

With hope, effort and luck, we can see the light, like Dr Menelik Lee, who managed to capture a nice photo of Aurora as shown on the cover of this March issue. I wish all of you and your family 'Stay safe and healthy'!

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Mid-trimester Morphology Scan and Beyond

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INTRODUCTION

The overall incidence of foetal structural abnormalities is around 2-3%.[1] Ultrasound screening for foetal abnormalities is an important part of routine antenatal care, providing an early opportunity for further counselling and management. The detection rate of foetal abnormalities by ultrasound varies, depending on gestational age, organ system, anatomy survey protocol, maternal size, ultrasound equipment and setting, operators' skills, and scanning time.[2] With advances in the technology of ultrasound, and the increasing expertise of operators, detailed examination of the foetal brain, heart, face and other structures is feasible, allowing early diagnosis and management.[2] The introduction of non-invasive prenatal testing (NIPT) with cell-free foetal DNA has a significant impact on the role of nuchal translucency scan and genetic sonogram regarding trisomy 21 detection.[3,4]

FIRST TRIMESTER

Regardless of whether a woman opts for NIPT or a combined first-trimester screening for Down syndrome, a scan should be offered to assess the foetal structures, among other reasons.[5] The important structures that should be assessed on the first-trimester scan are listed in the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) practice guidelines.[6] Additional examination of the posterior fossa, upper lip and palate, colour Doppler examination of the heart, and foetal echocardiography as appropriate, can improve the detection of anomalies of these structures, especially in the at-risk pregnancies.[7,8] Overall, a detailed examination of foetal structures in the first-trimester can allow early detection of about half of all major structural anomalies.[9] However, the first-trimester scan cannot replace the mid-trimester morphology scan because some major anomalies (such as absent corpus callosum or cerebellar hypoplasia) would only be detectable after the first-trimester.[2,10]

MID-TRIMESTER

For routine morphology scan at 18-22 weeks, the basic and optional foetal structures that should be examined are recommended in the ISUOG practice guidelines.[11] The reported detection rates for major anomalies vary hovering around 60%.[2,12] For detailed diagnostic ultrasound examination for at-risk pregnancies, assessment of additional foetal cardiac, brain, facial, and other structures is recommended in the recent AIUM guidelines.[13] At-risk pregnancies include, among other conditions, age 35 or above, gestational diabetes, assisted reproduction technology, body mass index >=30, teratogen, and nuchal translucency >= 3mm.[13]

Central nervous system anomalies are common, and are associated with aneuploidies, syndromes and neurodevelopmental delay. Recently, ISUOG has published indications for foetal targeted neurosonography.[14] In addition to the structures examined in the three standard transverse planes during basic ultrasound assessment, a targeted neurosonography involves a systematic examination with additional coronal planes through anterior and posterior fontanelles, and mid-and para-sagittal planes.[14,15] The anterior and posterior complexes of the foetal brain, including cavum septum pellucidum and corpus callosum, can be examined in detail for the detection of midline and cortical anomalies.

Given a low-risk NIPT result, the detection of isolated soft markers such as choroid plexus cyst or echogenic intracardiac focus is of little clinical significance.[4] However, further workup is still indicated for echogenic bowel, short long bones and dilated renal pelvis because of the risks of congenital infection, skeletal dysplasia, and urinary tract obstruction, respectively[4]. Furthermore, the definitions of soft markers vary among reported series.[16] In particular, absent nasal bone, aberrant right subclavian artery, and thick nuchal fold have been regarded by some clinicians as anomalies rather than soft markers; these anomalies should require further evaluation.[4,16]

THIRD TRIMESTER

According to a large retrospective study, 27.6% and 53.8% of non-chromosomal foetal abnormalities were detected in the first-trimester and mid-trimester scan, respectively, while 18.6% were detected in the third trimester or after birth.[7] Additional scan is thus required in the third trimester to increase the prenatal detection rate. AIUM suggests detailed diagnostic ultrasound examination in the third trimester, in addition to the mid-trimester ultrasound, for at-risk pregnancies.[13] According to a recent study, routine ultrasound examination at 35-37 weeks can, among other benefits, allow detection of a previously undiagnosed foetal abnormality (such as microcephaly, ventriculomegaly or coarctation of the aorta) in around 0.5% of pregnancies.[17] Such diagnosis may affect the timing and location for delivery and postnatal investigations.

NEW ULTRASOUND TECHNOLOGY

The use of three-dimensional (3D) ultrasound may help in the prenatal diagnosis of some anomalies, including facial clefts, micrognathia, and club feet.[2] New 3D ultrasound technologies include a special mode to enhance visualisation of the corpus callosum, and automatic measurement of head parameters, trans-cerebellar diameter, cisterna magna, and atrium of the lateral ventricle after 3D volume acquisition.[18] However, further studies are required to assess their effectiveness. Speckle tracking analysis of multiple cardiac ventricular measurements is a new way of evaluation of ventricular contractility, and may help improve detection of coarctation of aorta prior to delivery.[19]

CONCLUSION

Despite NIPT's advances in detecting chromosomal abnormalities, ultrasound screening for foetal structural anomalies is still required across all the trimesters.[2] With increasing expertise and routine use of the standard protocol, anomalies can be diagnosed with more certainty and at an earlier gestational age than ever before.[2,7] Foetal echocardiography and targeted neurosonography can be added as appropriate for the examination of at-risk pregnancies.[8,15]

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dTap vaccine with pregnancy safety & effectiveness data on label.[1-2*]

dTap = Tetanus toxoid, reduced diphtheria toxoid & acellular pertussis

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- **Hong Kong Centre for Health Protection** recommends Maternal Immunization with a dTap vaccine during 2nd - 3rd trimester.[5]

Boostrix should be administered in accordance with local official recommendations.[1]

Safety Information:[1]

The use of ***Boostrix*** may be considered during the third trimester of pregnancy. Human data from prospective clinical studies on the use of ***Boostrix*** during the first and second trimester of pregnancy are not available. However, as with other inactivated vaccines, it is not expected that vaccination with ***Boostrix*** harms the foetus at any trimester of pregnancy. The benefits versus the risks of administering ***Boostrix*** during pregnancy should be carefully evaluated.

* In Hong Kong Market as of Dec 2019

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Abbreviated Prescribing Information

Name of the Medicinal Product: *Boostrix*. **Qualitative and Quantitative Composition:** 1 dose (0.5 ml) contains not less than 2 IU diphtheria toxoid, not less than 20 IU of tetanus toxoid, 8 mcg of pertussis toxoid, 8 mcg of filamentous haemagglutinin, 2.5 mcg of pertactin, adsorbed on aluminium hydroxide, hydrated and aluminium phosphate. **Indications:** Indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards. **Posology and Administration:** A single 0.5 ml dose of the vaccine is recommended. The use of *Boostrix* may be considered during the third trimester of pregnancy. **Method of administration:** *Boostrix* is for deep intramuscular injection, preferably in the deltoid region. **Contraindications:** Subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines; Subject has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine. Administration should be postponed in subjects suffering from acute severe febrile illness As with other vaccines, administration of *Boostrix* should be postponed in subjects suffering from acute severe febrile illness **Special Warnings and Precautions for Use:** If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give doses of pertussis-containing vaccines should be carefully considered: temperature of ≥ 40.0°C within 48 hours of vaccination, not due to another identifiable cause; collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination; persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination; convulsions with or without fever, occurring within 3 days of vaccination. *Boostrix* should under no circumstances be administered intravenously. Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints. As with any vaccine, a protective immune response may not be elicited in all vaccinees. **Interactions:** If *Boostrix* is to be given at the same time as another injectable vaccine or immunoglobulin, the products should always be administered at different sites **Fertility, pregnancy and Lactation:** ***Pregnancy:*** The use of *Boostrix* may be considered during the third trimester of pregnancy. Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with *Boostrix* during pregnancy. The clinical relevance of this observation is unknown. **Breastfeeding:** The effect of administration of *Boostrix* during lactation has not been assessed. Nevertheless, as *Boostrix* contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering *Boostrix* to breastfeeding women should carefully be evaluated by the health-care providers. **Adverse Reactions: Clinical Trial Data:** *Children from 4 to 9 years of age* upper respiratory tract infection; anorexia; irritability; somnolence, headache and disturbances in attention; conjunctivitis; diarrhoea, vomiting, gastrointestinal disorders; rash; injection site reactions (including pain, redness and swelling), fatigue, fever ≥ 37.5 °C (including fever > 39 °C), other injection site reactions (such as induration) and pain. *Adults, adolescents and children from the age of 10 years onwards:* upper respiratory tract infection, pharyngitis; lymphadenopathy; headache, dizziness, syncope; cough; nausea, gastrointestinal disorders, diarrhoea, vomiting; hyperhidrosis, pruritus, rash; arthralgia, myalgia, joint stiffness, musculoskeletal stiffness; injection site reactions (including pain, redness and swelling), fatigue, malaise, fever ≥ 37.5°C, injection site reactions (such as injection site mass and injection site abscess sterile), fever > 39 °C, influenza like illness and pain. Data on 146 subjects suggests a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedules in adults (>40 years of age). ***Post Marketing Data:*** Angioedema, allergic reactions, including anaphylactic and anaphylactoid reactions, convulsions (with or without fever), urticaria, extensive swelling of the vaccinated limb, asthenia. **Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong.** Abbreviated Prescribing Information prepared in 11 Feb 2020 based on version HK022019 (GDS10/IPI11/MHRA20181214). For adverse event reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or (853) 2871 5569 (Macau), or send an email to us at HKAdverseEvent@gsk.com.

PM-HK-BOO-ADVT-190001 (01/2022) Date of preparation: 01/02/2020

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Optimal Management of Pregnant Hepatitis B Carriers to Achieve Complete Eradication of Hepatitis B Infection in Hong Kong

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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 March 2021.

BACKGROUND

Hepatitis B virus (HBV) infection continues to pose significant public health burdens worldwide. Chronic carriers are at risk of cirrhosis and hepatocellular carcinoma. Regular surveillance is recommended for early management to reduce the associated morbidity and mortality. In Hong Kong, an area of high HBV endemicity, chronic HBV infection is usually acquired during the perinatal period via vertical transmission from their carrier mothers. The female offspring then becomes pregnant in adulthood and transmits the HBV to their children perpetuating HBV infection in the community. Therefore, it is critical to break this vicious cycle. It is World Health Organization's (WHO) goal to eliminate HBV disease by 2030, defined as a 90% reduction in incidence and a 65% reduction in liver-related mortalities from the 2015 baseline.[1] This review will summarise the evidence-based interventions to reduce vertical transmission as well as the current preventive strategies in Hong Kong.

FACTORS AFFECTING VERTICAL TRANSMISSION OF HBV

Majority of the vertical transmission occurs during delivery when the newborn passes through the birth canal and contracts HBV from the maternal vaginal secretions, leading to chronic infection. Up to 90% of newborns could become chronically infected, whereas only 2% of adults become chronically infected after an HBV exposure.[2] Other factors can also affect the likelihood of chronic infection in newborns, including the maternal hepatitis B e antigen (HBeAg) status, maternal HBV DNA level, timing of birth dose HBV vaccination and availability of birth dose hepatitis B immunoglobulin (HBIG) injection.[3]

Universal hepatitis B surface antigen (HBsAg) testing of pregnant women can identify undetected chronic carriers and offer interventions to reduce the risk of HBV vertical transmission to their newborns. The combination of birth dose HBIG injection and a completed course of HBV vaccination remains the most effective intervention to prevent neonatal infection. In carriers seropositive for HBeAg, HBV vaccination alone reduces the risk of vertical transmission from 90% to 21%, and the addition of birth dose HBIG further decreases the risk to 6%. In carriers seronegative for HBeAg, the risk is reduced from 30% to 2.6% after HBV vaccination and is further reduced to 1% after HBIG.[4] Delayed birth dose vaccinations reduce the efficacy to prevent vertical transmission.[5] Immunoprophylaxis failure (IF) refers to persistent neonatal HBV infection despite optimal active and passive neonatal immunisation. Possible causes of IF include germline infection from infected sperm and ovum, invasive prenatal tests that lead to inoculation of HBV and transplacental HBV infection.[6] These in-utero infections could account for the residual HBV incidence in the era of universal neonatal HBV vaccination. Active viral replication reflected by positive HBeAg and elevated HBV DNA in the mother indicates a higher chance of IF through these mechanisms, providing a rationale to use antenatal antiviral treatment to suppress viral activity during pregnancy.[6]

MATERNAL ANTIVIRAL TREATMENT TO PREVENT IMMUNOPROPHYLAXIS FAILURE

Lamivudine, telbivudine and tenofovir disoproxil fumarate (TDF) are commonly used antiviral treatments during pregnancy.[7] TDF is the treatment of choice given its high potency and strong barrier to resistance.[8,9]

In an open label randomised controlled trial, 200 HBV carriers seropositive for HBeAg with a baseline viral load > 200,000 IU/ml (equivalent to 5.3 log10 IU/ml) were randomised to receive the usual antenatal care either without or with TDF from 30-32 weeks of gestation. TDF significantly reduced both the maternal HBV DNA at delivery and the rate of IF (intention to treat analysis 5% versus 18%, p = 0.007; per protocol analysis 0% and 7%, p = 0.01).[10]

Another double-blinded placebo-controlled trial randomised 331 seropositive HBeAg HBV carriers (approximately 90% had HBV DNA >200,000 IU/ml) to receive TDF or placebo from 28 weeks of gestation. The rate of IF was comparable (0% [0/147] in TDF group vs 2% [3/147] in placebo group, p = 0.12).[11] The low IF in both groups could be attributable to the inclusion of women with lower viral loads hence negligible risks of IF even without maternal antenatal antiviral treatment as well as the timely birth dose HBV vaccination and HBIG injection (median time was approximately 1.3 hours after birth).[12]

Teratogenicity of TDF has not been observed in the international registry which prospectively followed cases including first trimester exposure.[13] A systematic review also found no associated teratogenicity and other maternal or neonatal complications.[7] Cessation of TDF after delivery could result in a self-limiting asymptomatic hepatic flare, but there were no other major maternal or neonatal adverse effects.[10,11] Breastfeeding should be compatible as TDF was only present minimally in breastmilk, rendering breastfeeding while on TDF unlikely to cause serious toxicity.[14]

STRATEGIES EMPLOYED IN HONG KONG TO PREVENT MOTHER TO CHILD HBV TRANSMISSION

In Hong Kong, HBV vaccination and HBIG injection were first introduced to the newborns of carrier mothers in 1984. Universal neonatal HBV vaccination has been extended to all newborns since 1988. The coverage rate of three doses of HBV vaccination among children aged 3-5 was > 99%, leading to a gradual and sustained reduction in the local prevalence of HBV carriers.[15] For instance, the prevalence of pregnant HBV carriers dropped significantly from 11.3% to 4.5% between 1990 and 2018. An earlier study found that the rate of IF in 2000 was 2.5% (3/121).[16] Our group carried out a prospective multicentre observational study on 2014 to 2016 cohorts and found a further reduced IF rate of 1.1% (7/641). A positive HBeAg status and high level of HBV DNA ≥ 7.2 log10 IU/ml were significant predictors of IF (4.5% vs 0%, and 5.8% vs 0%, respectively; $P < 0.0001$).[17]

In the past, HBV DNA was not routinely examined during pregnancy, missing the opportunity to identify women at risk of IF. Multidisciplinary care involving hepatologists and obstetricians could optimise the management of HBV during pregnancy by timely disease assessment, monitoring, and jointly educating women on the safety and efficacy of antiviral treatment during pregnancy. Unfortunately, up to 86.4% of pregnant carriers in Hong Kong did not receive any medical care for HBV during pregnancy.[18] In 2017, an enhanced service model of testing HBV DNA levels during pregnancy and referring women with a viral load > 200,000 IU/ml to hepatologists for antiviral treatment was established at Queen Mary Hospital. 22.6% (60/265) of carriers had a high viral load, and the acceptance rate of this programme was 97.8%.[19]

In 2020, to strengthen the prevention of HBV vertical transmission, the Hospital Authority introduced early pregnancy HBV DNA quantification for all pregnant carriers and timely referral of women with a high viral load (> 200,000 IU/ml) to hepatologists for consideration of antiviral treatment from 28 weeks of gestation in all birthing hospitals. Unfortunately, the provision of post-vaccination serologic testing to all infants born to HBV carriers has not yet been established, but this is extremely vital for examining the effectiveness of this programme, allowing facilitation of early monitoring in infants with IF and providing a booster HBV vaccine to vaccine non-responders.

SPECIAL CONSIDERATIONS

Although third trimester use of TDF could prevent most IF, earlier treatment starting from the second trimester may be required in certain clinical conditions. An extremely high viral load at baseline (> 8 log10 IU/mL) could lead to suboptimal viral suppression and is associated with persistent IF (3.1%, 2/65) despite TDF treatment.[20] Preterm birth can also cause insufficient viral suppression due to the shortened antiviral treatment duration. Meta-analyses have suggested that HBV infection during pregnancy may increase the risk of preterm birth.[21] Therefore, women with an extremely high viral load (> 8 log10 IU/mL) or at risk of preterm birth (asymptomatic short cervix at second trimester or history of preterm birth) with a viral load > 200,000 IU/ml may benefit from earlier antiviral treatment starting from second trimester. In addition, amniocentesis could increase the risk of IF in women with a high viral load (i.e. ≥ 7.0 log10 IU/ml or 7 log10 copies/ml).[22,23] Relevant mothers should be informed of this risk. TDF treatment prior to amniocentesis could be considered, and the alternative of non-invasive prenatal testing should be explored.

CONTROVERSIES AND RESEARCH

The viral load cut-off to start antiviral treatment has been controversial and varies among international authorities.[24-26] Until recently, the WHO published recommendations that a cut-off of 200,000 IU/mL should be used (moderate quality of evidence) and is presently adopted by the Hospital Authority.[27] However, the negative result by Jourdain et al. and our local study (which showed the lowest maternal viral load for IF was 7.9 log10 IU/ml) suggest a higher local viral load cut-off may be utilised under a comprehensive and well-structured immunisation programme in Hong Kong.[11,17] We initiated a study group consisting of obstetricians, hepatologists and paediatricians to prospectively assess the rate of IF following this newly implemented Hospital Authority programme. We will evaluate the factors associated with IF despite maternal TDF treatment (i.e. baseline maternal HBV DNA level, duration of antiviral treatment, timing of birth dose vaccination, duration of labour and invasive prenatal testing) and the pregnancy outcomes in women with different HBV DNA levels. These data are imperative to further enhance the management of pregnant HBV carriers and to reduce the IF rate.

CONCLUSION

Besides neonatal vaccination, maternal HBV DNA quantification and antiviral treatment become another cornerstone in reducing mother-to-child transmission during pregnancy. Pregnant carriers should receive multidisciplinary care for HBV disease assessment, and neonates should be given timely vaccination. With concerted efforts from various stakeholders and local academics, I have no doubt that Hong Kong will be taking the lead in achieving complete eradication of HBV diseases in near future.

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Dermatology Quiz

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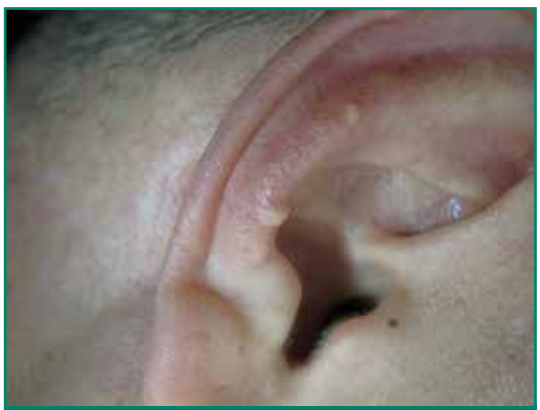

Fig.1. Pale yellowish lumps on the right pinna.

Case history:

This 46-year-old gentleman complained to have two pale yellowish papules on the right pinna for one year. The onset was insidious, and the size seemed static. There was no bleeding and the lesions were not painful. There was no history of injury before. Physical examination revealed two 2-3 mm well-defined pale yellowish papules on the right pinna. There was no ulcer nor erosion (Fig. 1).

Questions

1. What are the differential diagnoses of his skin lesions?
2. What investigation are you going to order?
3. How do you treat this patient?

(See P.40 for answers)

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	safe21	OSCAR	Karyotyping Analysis / FISH / CMA	
Test Type	Screening Test	Screening Test	Diagnostic Test	
Sample Type	Blood	Blood	Chorionic Villus	Amniotic Fluid
Gestational Age	≥Week 10 Twins ≥Week 12	Week 11-14	Week 11-13	Week 16-22
Miscarriage Risk	No	No	0.1-0.2%	0.1-0.2%
Turnaround Time (Working Days)	About 5 days	1-2 days	7-15 days	7-15 days
Testing Item				
Trisomies	✓	✓	✓	✓
Sex Chromosome Aneuploidies	✓		✓	✓
Microdeletions Screening	✓		✓	✓

Compared to the traditional Down Syndrome screening, safe21 has a higher accuracy. This has reduced the need for invasive procedures (performed in Hong Kong) such as Chorionic Villus Sampling (CVS) or Amniocentesis (Amnio) by almost 30%[1,2], minimizing the unnecessary risk of miscarriages.

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Since our establishment, Xcelom has gained extensive support from the public for the services offered by our team of experts and state of the art laboratory. Xcelom will strive to improve and expand the spectrum of services offered, to continue to provide well-rounded care for our client's health.

Reference:
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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Optimal Management of Pregnant Hepatitis B Carriers to Achieve Complete Eradication of Hepatitis B Infection in Hong Kong" by Dr CHEUNG Ka-wang 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 March 2021. 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. The risk of acquiring chronic infection is the highest after perinatal exposure.
2. Delaying the birth dose HBV vaccination will increase the risk of immunoprophylaxis failure.
3. Hepatitis B immunoglobulin vaccination should not be given to newborns of carrier mothers.
4. The local incidence of immunoprophylaxis failure is approximately 1.1%.
5. Maternal HBV DNA should be used to guide maternal antiviral treatment to prevent immunoprophylaxis failure.
6. Maternal hepatitis e antigen status should be used to guide maternal antiviral treatment to prevent immunoprophylaxis failure.
7. A maternal viral load cut-off of 200,000 IU/ml is currently adopted by the World Health Organization and Hospital Authority to initiate antiviral treatment to prevent immunoprophylaxis failure.
8. Tenofovir disoproxil fumarate is the suggested antiviral agent to prevent immunoprophylaxis failure.
9. Breastfeeding is contraindicated to women taking tenofovir disoproxil fumarate.
10. Amniocentesis in carrier mothers with the low viral load will not increase the risk of immunoprophylaxis failure.

ANSWER SHEET FOR MARCH 2021

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Optimal Management of Pregnant Hepatitis B Carriers to Achieve Complete Eradication of Hepatitis B Infection in Hong Kong

Dr CHEUNG Ka-wang

Consultant
Department of Obstetrics and Gynaecology, Queen Mary Hospital, the University of Hong Kong, Hong Kong SAR, China.

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

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

Answers to February 2021 Issue

Acute Arthritis in Children

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

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Reference
1.Hurtado JA et al. Oral administration to nursing women of *Lactobacillus fermentum* CECT5716 prevents lactational mastitis development: a randomized controlled trial. Breastfeed Med. 2017;12: 202-209.
* Studied population: 625 women participated who received preventive antibiotics between 48 hours before and after childbirth
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The Establishment of the FMPRG (+ website) and the Way Forward

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Dr LEUNG Wing-cheong Dr NG Wai-fu

INTRODUCTION

A multidisciplinary approach to managing the abnormal foetus, an approach which provides the best outcome in diagnosis, management and counselling to the family, has been well established.[1,2] This article introduces the establishment of the multidisciplinary team of FMPRG as a pilot study to explore such a model from 2019 onwards. An illustrative case demonstrating the multidisciplinary teamwork in the work-up and diagnosis of the case is described. The preliminary results are presented and the way forward explored.

THE ESTABLISHMENT OF FMPRG

The Hong Kong Children's Hospital (HKCH) commenced its services in 2018. It operates under a hub-and-spoke model consisting of regional hospitals and a tertiary referral centre for complex, serious and uncommon paediatric cases requiring multidisciplinary management.[3] With the special approval from the Hospital Chief Executive and the Head of the Department of Pathology, the second author (WF Ng) started a pilot foetal pathology service from 2019 onwards. FMPRG is the abbreviation for the multidisciplinary team made up by the following specialties: Foetal Medicine, Pathology, Radiology and Genetics. This abbreviation was coined by the Kwong Wah Hospital (KWH) Maternal Foetal Medicine (MFM) Team.

The team comprises 31 members (up to Dec 2020) including

- MFM subspecialists/obstetricians from four obstetric departments (KWH, QEH, QMH/TYH and UCH);
- Clinical geneticist from the Clinical Genetic Service of the Department of Health;
- Scientific officer from Prenatal Diagnostic Laboratory of QMH/TYH
- Personnel from HKCH:
  - paediatricians of the Neonatal Intensive Care Unit
  - radiologists with a special interest in perinatal imaging (MRI, etc.)
  - scientific officers and pathologists of Genetic and Genomic Pathology and Anatomical Pathology.

Complex foetal cases that need detailed pathological examination and multidisciplinary consultation are referred from KWH, QEH and UCH to HKCH Anatomical Pathology. After pathological work-up, the cases with the clinical information, annotated radiology and pathology images are put up in the FMPRG platform for discussion, for correlation with genetic findings if available, for the decision on follow-up actions and for serving as an education platform. The platform for communication was initially based on e-mailing among the group members. In Oct 2020, a pilot web-based platform (Fig. 1) was established under the Department of Pathology of HKCH. There is a depository site for uploading the active cases for discussion and management decision, as well as an archival site for old cases for education. The website and its application are now undergoing trial and evaluation.

Although the project was initially designed for the foetus of not more than 24-week gestation with the termination of pregnancy, cases of intrauterine death (more than 24-week gestation) and neonatal death have been included. Due to the limitation that the mortuary of HKCH is not equipped to do autopsies, these autopsies were done in the regional hospitals by the second author (WF Ng). An illustrative case (with the couple's consent) of foetal alloimmune thrombocytopenia (FAIT) with intracerebral haemorrhage in a 27th week early onset intrauterine growth retarded (IUGR) foetus is presented in the following. The multidisciplinary discussion & input by FMPRG confirmed the diagnosis of FAIT and helped to plan for the management of the next pregnancy.[4-10]

CASE PRESENTATION

This was the first pregnancy belonging to a Chinese non-consanguinous couple. Our patient, the wife, had a history of warm autoimmune haemolytic anaemia with splenomegaly, earlier presenting with anaemic symptoms with dark coloured urine. Her haemoglobin level could be as low as 5 g/dl requiring blood transfusion. She was treated with Prednisolone.

For the index pregnancy, the first trimester Down screening showed low risk (1 in 433). Non-invasive prenatal test (maternal plasma-free foetal DNA) also showed a low risk of common aneuploidies. Foetal anomaly ultrasound examination at 20 weeks' gestation showed the foetus had short limbs. The foetus was diagnosed to have early onset intrauterine growth retardation since 22 weeks with an estimated

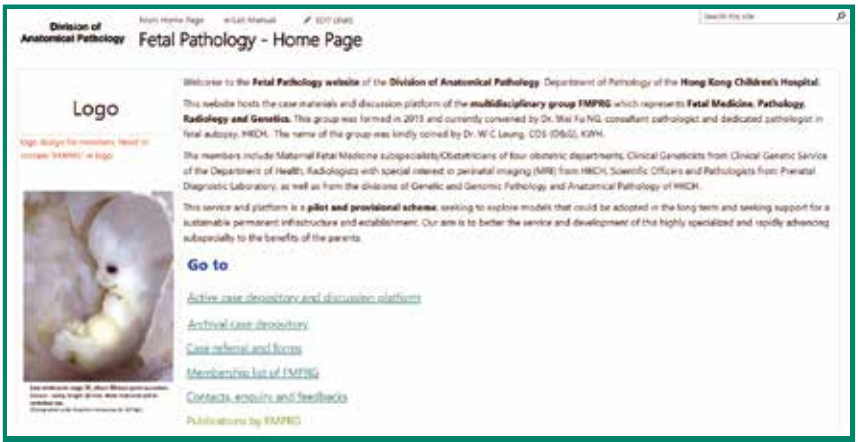

Fig. 1. FMPRG website (Excerpted from http://hkch.home/hospital/hospital.aspx)

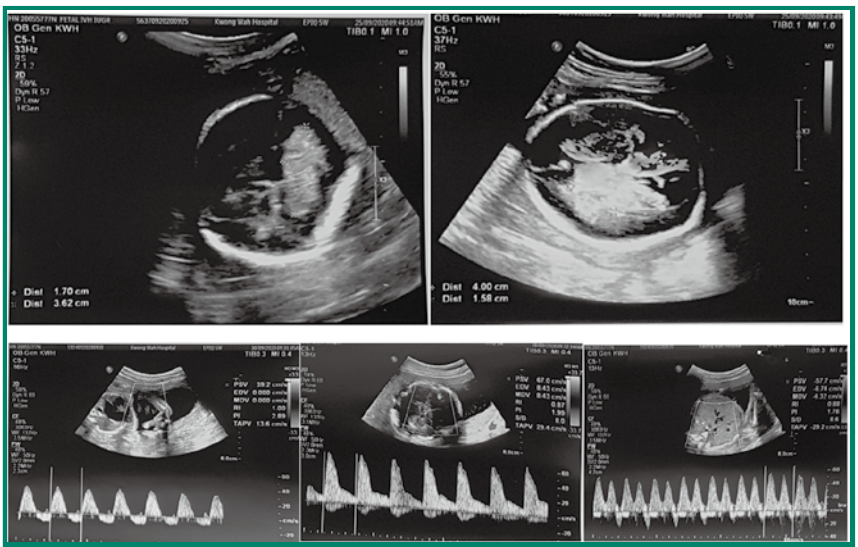

Fig. 2. Ultrasound showing foetal intraventricular haemorrhage and abnormal Doppler ultrasound (27 weeks' gestation) (Photos from the personal collection of the first author WC Leung)

Upper left: left-sided foetal intraventricular haemorrhage (IVH) (coronal plane)
Upper right: left-side foetal IVH (axial plane)
Lower left: Umbilical artery → reversed end-diastolic flow
Lower middle: Middle cerebral artery peak systolic velocity → >1.5 MoM → foetal anaemia
Lower right: Ductus venosus → reduced / reversed "a" wave

foetal weight of 343 gm, short limbs, and ultrasound Dopplers examination showing foetal-brain sparing & right-sided uterine artery notching. Doppler studies further deteriorated at 26 to 27 weeks (Fig. 2). The estimated foetal weight was only 564 gm. Congenital infection screen was negative. The patient was admitted to the hospital for corticosteroid prophylaxis in case preterm delivery was required. Repeated ultrasound examination showed massive left-sided foetal intraventricular haemorrhage with high peak flow velocity inside the foetal middle cerebral artery suggestive of foetal anaemia (Fig. 2).

Platelet immunology studies of the couple showed the presence of maternal anti- human platelet antigen (HPA)-5b antibodies against paternal HPA-5b antigen (heterozygous). Genotyping by polymerase chain reaction sequence-specific primer (PCR SSP) showed maternal 5aa and paternal 5ab. There was also the presence of maternal IgG autoantibody against maternal platelets (Glycoprotein IIb/IIIa), but the contribution to foetal thrombocytopenia was usually mild.

The couple opted for conservative management of the pregnancy in view of the guarded foetal prognosis. Intrauterine death of the foetus was confirmed at 28 weeks. The stillbirth was delivered after medical induction with two doses of prostaglandin E2. The delivery was difficult in breech presentation with entrapment of the aftercoming head. The stillbirth weighed 511 gm.

The placental tissue for chromosomal microarray showed no copy number gain or loss and an XY genotype. The HPA genotyping by multiplex PCR followed by fluorescence monitoring to detect HPA alleles showed the placental DNA was HPA-5ab, i.e. the same as the paternal HPA.

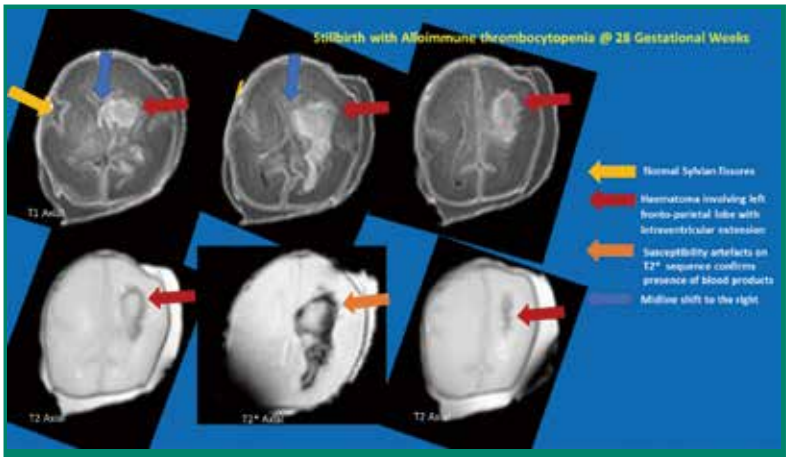

Fig. 3. Postmortem MRI (Photos from Elaine Kan's personal collection)

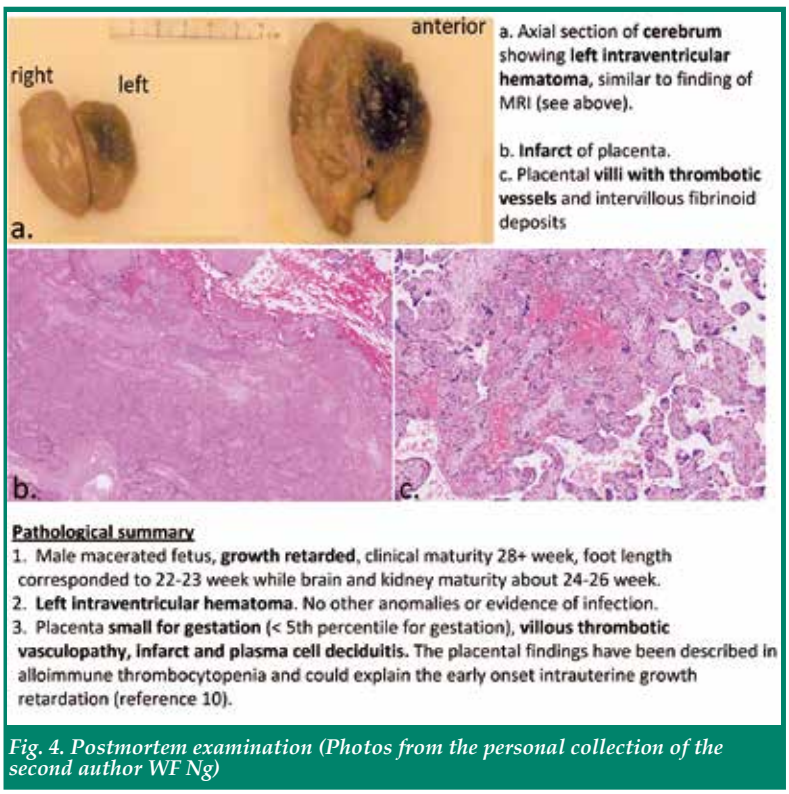

Fig. 4. Postmortem examination (Photos from the personal collection of the second author WF Ng)

Postmortem MRI (Fig. 3) and detailed autopsy (Fig.4) were performed. The placenta weighed 250 gm. Histopathology of placenta showed foetal thrombotic vasculopathy, focal infarct and intervillous thrombi (Fig. 4).

Multidisciplinary discussion and input by FMPRG confirmed the diagnosis of foetal alloimmune thrombocytopenia (FAIT) with intracerebral haemorrhage in a 27th week early onset intrauterine growth retarded foetus.

Concerning future pregnancy for this couple, there was a 50% risk of another HPA-5ab foetus. One possible solution would be preimplantation genetic testing for monogenic disease (PGT-M) to exclude the paternal allele of HPA-5b; there would then be a 50% chance to have transferrable embryos, i.e. HPA-5aa embryos. After getting pregnant, chorionic villus sampling or amniocentesis can be performed for foetal HPA genotyping to confirm foetus HPA-5aa status. The option of the bespoke non-invasive prenatal test (maternal plasma-free foetal DNA) to detect any presence of HPA-5b can be explored. On the other hand, if the patient is carrying an HPA-5ab foetus again, weekly intravenous immunoglobulins can be considered from 16 weeks onwards to prevent foetal occurrence of intracerebral haemorrhage again.

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+ Abbott Similac® Mom contains most of the nutrients mentioned in National Institutes of Health (NIH) on the important maternal nutrients during lactation, including protein, DHA (12.5mg/100ml), folic acid, and 18 vitamins and minerals. Suggest to have 2 servings per day with a balanced diet, while staying active and relaxed to support breastfeeding.

* HMO : Human Milk Oligosaccharide 2'-FL (20 mg / 100ml), not from Human milk

^ NTs: Nucleotides (2.9 mg / 100ml)

圖片僅供參考。

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FM (Foetal Medicine) - MFM Team, Dept of O&G, Kwong Wah Hospital, Hospital Authority, HKSAR
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P (Pathology) - Dr WF Ng, HKCH
R (Radiology) - Dr Elaine Kan, HKCH
G (Genetics/Genomics) - Prof Richard Choy, CUHK

PRELIMINARY RESULTS OF FMPRG

A total of 21 cases were provided FMPRG care, 14 in 2019 and 7 in 2020 up to 30th November. These cases are summarised in Table 1.

Table 1. Summary of foetal cases examined by FMPRG according to action categories. (Summarised by Dr WF Ng)

Group 1: Diagnosis confirmed by multidisciplinary consultation and genetic testing not proceeded (5 cases)	• Neural tube defect, sporadic (2 cases) • Thanatophoric dysplasia (declined chorionic villus sampling) • Treacher Collin syndrome (known diagnosis in mother) • Early onset intrauterine growth retardation due to maternal floor infarct of the placenta
Group 2: Abnormal foetus confirmed by multidisciplinary consultation and genetic test not proceeded due to various reasons (6 cases)	• Dysmorphic macerated foetus • Radial bone aplasia (mother lost to follow up) • Mid-trimester missed abortion • Potter sequence and Tetralogy of Fallot • Arachnoid cyst of brain • Shortened long bones but not definite for skeletal dysplasia
Group 3: Specific diagnosis arrived with multidisciplinary consultation and genetic testing (6 cases)	• Cornelia de lange syndrome (NIPBL gene)[1] • Osteogenesis imperfecta (COL1A1 gene)[2] • Apert syndrome (FGFR2 gene)[2] • Cutis laxa (PYCRI gene)[2] • Bilateral microphthalmos and microcephaly (OCLN gene)[3] • Intrauterine death due to alloimmune thrombocytopenia (anti-HPA-5b)[4]
Group 4: Abnormal foetus confirmed by multidisciplinary consultation and genetic testing in progress (4 cases)	• Hydropic intrauterine death • Skeletal dysplasia (2 cases) • Cerebral cortical malformation, suggestive of polymicrogyria
	Total 21 cases

(1) Medical exome sequencing, Clinical genetic service, Department of Health
(2) Trios Whole exome sequencing, TYH/ QMH
(3) Whole genome sequencing, CUHK, OBS research
(4) HPA genotyping, Haematology, QMH; Prenatal Diagnosis Laboratory, CUHK

THE WAY FORWARD

FMPRG is a pilot project, and the work has been done out of dedication by the concerned members. A yearly approval is sought from the hospital and is effective till the end of 2020. Extension of this pilot is subject to the consideration of the manpower issue. The concerned parties are exploring submitting a multidisciplinary annual plan bid to the Hospital Authority to secure funding for establishing a sustainable clinical service.

The authors strongly recommend that FMPRG should be extended to become a territory-wide multidisciplinary platform in order to benefit more families. Support from the Hospital Authority and other parties are urgently required.

Declaration: The views expressed in this manuscript represent only that of the authors.

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COVID-19 and Reproduction

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a pandemic of coronavirus disease 2019 (COVID-19), which has lasted nearly one whole year. Many countries are now experiencing another surge of the outbreak. As of 28th December 2020, there have been a total of 8,672 cases of COVID-19 in Hong Kong. Our daily activities have been greatly affected. Not only are we not allowed to dine in or visit cinemas and many other entertainment facilities, schools are closed, and many non-essential medical services are suspended. Many authoritative bodies including the European Society of Human Reproduction and Embryology (ESHRE), American Society for Reproductive Medicine (ASRM) and the International Federation of Fertility Societies (IFFS)[1,2] have advised that pregnancy be postponed during the pandemic, based on very limited data. Nearly all of the assisted reproductive technology (ART) services worldwide have been halted during the pandemic. Pregnant women are facing extra threats as they are regarded as a high-risk group and they carry the additional risk of transmitting the virus to their newborn babies in case they are affected[3,4]. In this short review, we aim to give the readers a glimpse of the current information on COVID-19 and reproduction, including the effect on gametes, pregnancy and ART.

COVID-19 AND MALE/FEMALE GAMETES

Overall we hold limited data on the impact of COVID-19 on male/female gametes, and we are uncertain of the impact. SARS-CoV-2 has been detected in semen[5], vaginal fluid and peritoneal fluid[6,7]. Angiotensin-converting enzyme 2 (ACE2) is required in the binding of SARS-CoV-2 spikes to hosts in order to trigger subsequent cascades of clinical events and damages. Expression of ACE2 has been shown in testicular and ovarian tissue[5,8], which may indicate the susceptibility of human gametes to SARS-CoV-2. Following binding to ACE2, transmembrane serine protease S (TMPRSS2) would trigger a conformational change to spikes enhancing fusion. However, the lack of co-expression of ACE2 and TMPRSS2 genes and proteins in testicular cells, sperms, ovarian somatic cells and oocytes may suggest that both male/female gametes and long term fertility are unlikely affected by SARS-CoV-2 infection[9].

COVID-19 AND PREGNANCY - MATERNAL RISK

Pregnant women are a susceptible high-risk group[3,4]. In the largest systematic review of COVID-19 pregnancy database (PregCOV-19LSR), a total of 35,392 infected pregnant women were reported from 55 studies spanning 16 countries[10]. The commonest symptoms of COVID-19 during pregnancy were cough, fever, followed by breathlessness and muscle ache[10]. The signs and symptoms were similar to their non-pregnant counterparts. About 4% of the infected pregnant women required admission to the intensive care unit, and 3% of them required invasive ventilation. Pregnant women were more likely to require admission to the intensive care unit (OR 1.62, 95% CI 1.33 - 1.96) and to require invasive ventilation (OR 1.88, 95% CI 1.36 - 2.60) when compared to non-pregnant women at reproductive age. As shown in a French study, pregnant women were five times more likely to be admitted to the intensive care unit as compared to non-pregnant women[11]. From case-control studies, COVID-19 disease manifestations in pregnant women in early gestation were not more severe than non-pregnant women[6]. However, women in later gestation were more frequently found to have severe disease. The median gestational age at hospitalisation was 34 weeks in the U.K. Obstetrics Surveillance System (UKOSS) study[12].

Non-comparative studies have shown a relatively high Caesarean section rate of up to around 60%[10], partly due to critical maternal condition and partly due to the intention to reduce maternal-to-fetal transmission, although statistically significant difference was not demonstrated between pregnant women with and without COVID-19 in comparative studies[10]. One fifth of them required general anaesthesia due to severe COVID-19 symptoms or urgency of birth[12]. The chance of prematurity was around 20%[10]. Mild COVID-19 infection was not associated with a higher chance of prematurity. However, when the women developed severe disease, there was usually a low threshold to consider delivery regardless of the gestational week.

COVID-19 AND PREGNANCY - FOETAL RISK

The risk of vertical transmission is present but low. From the PregCOV19LSR, 286 out of 3,132 neonates had suspected/confirmed COVID-19 infection. Potential vertical transmission of COVID-19 to infants has been reported[13,14]. While positive SARS-CoV-2 RT-PCR was shown in amniotic fluid, cord blood, vaginal fluid, neonatal plasma, neonatal anal or faecal samples in some studies[10], the absence of viral RNA in amniotic fluid, cord blood and breastmilk has been reported in others[15]. In view of this negative finding in breastmilk, the Royal College of Obstetricians and Gynaecologists still suggests that breastfeeding be continued as the benefits still outweigh the risks unless it is not possible due to severe medical conditions.

Despite the median gestational age at delivery being 34 weeks in the PregCOV19LSR cohort, which was not too premature, approximately 30% of neonates required admission to the neonatal unit[10]. Nevertheless, they reported insignificant risk of neonatal death and stillbirth, and > 95% of babies were in good condition at birth. In another review of 162 pregnancies, 38% of births were premature, 9% had intrauterine growth restriction, and the neonatal death rate was 2%[6].

COVID-19 AND ASSISTED REPRODUCTIVE TECHNOLOGY

Infertility, though classified as a disease, is never considered a medical emergency. During the pandemic, many ART services have been postponed due to (1) uncertainty of the impact of COVID-19 on fertility and (2) the overwhelmed medical system requiring extra medical manpower support. In addition, social distancing and avoidance of crowded places such as clinics/hospitals have been recommended. At the start of the pandemic, most ART services in both public and private sectors were ceased. Meanwhile, infertile women are constantly facing the natural decline of fertility with advancing age and are stressed after years of waiting beforehand. In later months, ART services have been gradually resumed. Our centres at Queen Mary Hospital and Kwong Wah Hospital have respectively continued ART services on a voluntary basis throughout the pandemic. Extra infection control precautions for patients visiting the clinics and closed system for storage of vitrified embryos are implemented in order to minimise infection risks and cross contaminations of different embryos.

Clinically, we have reviewed the pregnancy outcome of in-vitro fertilisation in our unit and have not identified any significant difference in the fertilisation rate, the number of embryos obtained and pregnancy outcome. Similar pregnancy outcome was observed in frozen-thawed embryo transfers as well. From the joint statement of ASRM, ESHRE and IFFS[1], proactive risk assessment, implementation of active risk mitigation strategies (e.g. reducing the patient load and spacing out appointments, limiting accompanying persons, patient and staff triage and testing, sanitation and proper use of personal protective equipment, use of telemedicine and freeze-all strategy for high-risk cases), as well as comprehensive counselling are recommended before resumption of ART services. ART centres should also be prepared to terminate their services in case of emergency.

As a result of limited medical resources during the pandemic, prioritisation of care needs to be carried out. Fertility preservation for oncological patients undoubtedly commands top priority. Women with advanced age or poor ovarian reserve also warrant prompt treatment. Other than these high priority groups, prioritisation becomes more difficult to be standardised, as the criteria may vary from centre to centre, and may also vary according to resources available.

ADAPTATIONS DURING THE PANDEMIC

Additional measures have been implemented to enhance the safety of medical staff and patients during the pandemic. Since 25th January 2020, the Hospital Authority in Hong Kong escalated the emergency response level from "serious" to "emergency". All patients and visitors are required to fill in health declaration before entering clinics/ hospitals. Body temperature is checked at every medical encounter. Extra social distancing measures are implemented, including spacing of chairs at waiting areas and the person-to-person distancing at queues. Everyone is required to wear face masks. The number of accompanying visitors during clinic sessions has been limited, and "husband accompanying birth" practices have been suspended in many public hospitals during outbreaks. In some clinics/hospitals, a negative COVID-19 test is required before medical consultations, especially for non-emergency services. Active influenza vaccination is promoted to avoid the worsening of mortality and morbidities in case of a double hit.

CONCLUSION

Although there have been many uncertainties about the impact of COVID-19 on reproduction and pregnancy, the maternal and foetal risks are uncommon, and the chance of long-term implication on fertility is probably small though not negligible. Extra vigilance should be exercised to reduce transmission and to enable identification of complications early. Looking forward to the launch of vaccination worldwide, we hopefully would be able to overcome this historic pandemic soon.

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Pertussis Vaccination During Pregnancy

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ABOUT PERTUSSIS

Pertussis (whooping cough) is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. The disease is acquired through droplets from coughs or sneezes or via direct contact with an infected person's respiratory secretion. The incubation period ranges from 4 to 21 days, usually 7 to 10 days. Pertussis can affect all ages, but infants are most vulnerable. The case fatality rate can be up to 4%.[1] While the disease is usually mild and symptoms are non-specific in adolescents and adults, infants and young children have a much greater risk of having severe complications, which could be fatal. An infected person may present with non-specific symptoms such as runny nose, cough and low grade fever. However, cough can gradually become more severe, with spells of violent coughing, affecting breathing. After coughing fits, patients often need to take deep breaths, which result in a "whooping" sound. These symptoms can last for several weeks. Complications include lung infection, seizures and brain damage.

RECENT DISEASE BURDEN IN HONG KONG

The pertussis-containing vaccine was first introduced in Hong Kong in 1957. Under the current Immunisation Programme, all children should receive six doses of pertussis-containing vaccines, i.e. three primary doses at two months, four months and six months of age, as well as three booster doses at 18 months of age, at Primary one and at Primary six.[2] The immunisation coverage of the 3-dose primary series and the booster doses of pertussis-containing vaccines have been maintained at a very high level of over 95%.[2]

Nonetheless, there has been an upsurge in the notified pertussis cases since 2017. The number of pertussis reported to the Centre for Health Protection (CHP) has been increasing: 5 cases in 2010, 20 cases in 2012, 30 cases in 2014, 31 cases in 2016, 69 cases in 2017, and 110 cases in 2018; the latter was the highest number recorded over the last few decades.[2] Between 2017 and 2018, 72 cases (40%) affected were infants below six months of age; 35 (20%) were infants below two months, who were not yet due for the first dose of pertussis-containing vaccine. There was also a small pertussis outbreak at the postnatal ward involving three neonates.

Meanwhile, there was also an increase in the proportion of adult infection between 2017 and 2018, accounting for about 50% of the cases recorded in 2017-2018 compared with 20-35% in 2013-2016.[3] The number of pertussis clusters also increased from fewer than 5 clusters in 2009-2016 to 7 in 2017 and subsequently 12 in 2018.[2] In the five years between 2014 and 2018, a total of 27 clusters were recorded by CHP. All were small clusters involving 2-4 cases while all except one cluster occurred in a household setting. Among the 60 cases in the household clusters between 2014 and 2018, 23 (38%) were infants below six months of age, while 30 (50%) were their mother or carer.[2]

In view of such a surge in pertussis cases in recent years, the Scientific Committee on Vaccine-Preventable Diseases of the CHP recommended antenatal pertussis immunisation in January 2019.[3] From July 2, 2020, antenatal pertussis vaccination was provided free to all pregnant women at the antenatal clinics of all birthing hospitals under the Hospital Authority (HA) and at the Maternal and Child Health Centres (MCHCs) under the Department of Health (DH).[4] Antenatal pertussis vaccination has become part of the routine antenatal care, regardless of prior pre-pregnancy vaccinations or any natural infection history against pertussis.

PERTUSSIS-CONTAINING VACCINATION

The pertussis-containing vaccine provided to pregnant women in the HA and MCHCs is Boostrix (dTap). The lower-case letters in these abbreviations "d" and "p" connote the smaller doses of diphtheria and pertussis in the vaccine; "a" stands for "acellular". The upper-case "T" means the vaccine has full-strength doses for that the tetanus part of the vaccine. Nevertheless, the antigen level for tetanus is still less than that of Infanrix Hexa (DTaP-IPV-HBV/Hib) and Infanrix-IPV/Hib (DTaP-IPV/Hib) used in the Childhood Immunisation Programme, as pertussis and diphtheria antigens. Through such vaccination, pregnant women will develop and pass the antibodies to the foetus before delivery, providing direct protection for infants against pertussis.

EFFECTIVENESS OF MATERNAL PERTUSSIS VACCINATION

Effectiveness of maternal immunisation for preventing pertussis in young infants has been documented in countries where maternal pertussis vaccination has been implemented. In UK, an emergency programme to offer pertussis vaccination (diphtheria-tetanus-5-component acellular - dT5aP-IPV) to pregnant

women was introduced in 2012, in response to a rise in hospitalisations and deaths among unimmunised infants < 3 months of age, with 14 pertussis-related infant deaths reported in the 2012 peak.[5] Vaccine effectiveness in the first year of the programme was estimated to be > 90% for infants < 2 months of age, whose mothers received vaccine at least one week prior to delivery, and could be sustained for at least three years following its introduction.[6,7]

Similar findings have also been reported in the U.S., suggesting additional protection for the first year of life on top of the childhood immunisation programme. In a retrospective cohort study of 148,981 infants born at Kaiser Permanente Northern California from 2010 to 2015, the vaccine effectiveness of maternal dTap was reported as 91.4% during the first two months of life and 69.0% during the entire first year of life.[8] The vaccine effectiveness was 87.9% before infants had any DTaP vaccine doses, 81.4% between doses 1 and 2, 6.4% between doses 2 and 3, and 65.9% after infants had 3 DTaP doses.[8] In another study comparing maternal dTap vaccination during pregnancy with that at the postpartum period in 74,791 live birth from the California Immunisation Registry between 2013 and 2014, dTap vaccination during 27-36 weeks' gestation was 85% more effective than postpartum Tdap vaccination in preventing pertussis in infants up to 8 weeks of age.[9] Even though an infant got infected with pertussis, the clinical course was significantly less severe among those whose mother was vaccinated during pregnancy.[10] In a cohort study reporting 752 infants infected with pertussis at younger than nine weeks of age, infants born to mothers who had received prenatal dTap had a significantly lower risk of hospitalisation (RR 0.41), ICU admission (RR 0.8) and shorter hospital stay (median 3 vs 6 days).[10] Australia's experience also showed that maternal dTap vaccination at 28-32 weeks of gestation carries 94% effectiveness at preventing severe disease in infants.[11]

RECOMMENDATIONS FROM THE WORLD HEALTH ORGANISATION, THE INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS, AND OVERSEAS PRACTICES

Because of the resurgence of pertussis in countries with high childhood vaccination coverage, such as Australia, Japan, the United States (US) and United Kingdom (UK), the World Health Organisation (WHO) updated her position paper on pertussis vaccines and recommended antenatal vaccination in 2015[12].

In 2006, the Advisory Committee on Immunisation Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended an approach to protect infants from pertussis infection through "cocooning".[13] Cocooning refers to vaccinating the mother at the postpartum period and all the family members including caregivers to form a protective cocoon of immunity around the newborn. Since 2011, ACIP started recommending a single dose of acellular pertussis vaccine combined with tetanus and diphtheria toxoid for all pregnant women during the third trimester of pregnancy, preferably at 27-36 weeks' gestation.[14]

In 2012, the Joint Committee on Vaccination and Immunisation (JCVI) in the UK introduced routine multivalent vaccine dTaP-IPV (i.e. low-dose diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated polio antigen) in pregnancy.[15] In the same year, the US ACIP updated their single-dose recommendation to recommend maternal acellular pertussis immunisation for each pregnancy.[14]

In Australia, the recommendation of cocooning, which had been adopted since 2003, was changed to antenatal immunisation at the third trimester of pregnancy in 2013. The optimal timing of vaccination was specified to between 28 and 32 weeks of gestation in 2015.[16-17] At the same time, the Australian Government also funded antenatal immunisation programmes throughout the continents between 2014 and 2015, and advanced the vaccination schedule to as early as 20 weeks' gestation in 2018.[18-19] In view of a major pertussis outbreak resulting in hundreds of infants requiring hospitalisation and two deaths from infants too young to be immunised, the New Zealand Ministry of Health started recommending antenatal vaccination at 28-38 weeks since 2012.[20-21] The latest vaccination schedule was updated to as early as 16 weeks of gestation.[22]

Among the European countries, Belgium, the Czech Republic, Ireland, Italy, Portugal, Slovenia and Spain of the European Union have introduced similar maternal vaccination programmes since 2012.[23] At present, Singapore and Taiwan are other Asian countries and regions which have also recommended antenatal pertussis vaccination.[24,25] The FIGO Committee for Safe Motherhood and Newborn Health Committee also endorsed this year the recommendations to vaccinate all pregnant women against dTap preferably between 27 and 36 weeks of gestation in each pregnancy.[26]

SAFETY OF MATERNAL PERTUSSIS VACCINATION IN PREGNANT WOMEN

There has been so far no adverse pregnancy outcome reported in countries where maternal dTap vaccination is routinely used for many years. In UK, the safety of pertussis vaccination, based on 20,000 pregnant women who had received the vaccine in the third trimester, was reported to show no evidence of an increased risk of stillbirth, nor maternal or neonatal morbidity and mortality.[27] In US, ACIP did not observe any unusual patterns of adverse events in pregnant women who received dTap or in their infants; a few adverse events reported were judged unrelated to the vaccine use.[28] Recent large cohort studies and systematic review also suggested no increase in the risk of foetal malformation, preterm delivery, low birth weight or postpartum infection.[29-33]

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IMMUNOGENICITY AND GESTATIONAL AGE OF VACCINATION

Antibodies against all *Bordetella pertussis* antigens have been shown to reach peak levels at the end of the second week after dTap administration in non-pregnant women of childbearing age, and this peak is followed by a rapid decline.[34] Studies in pregnancy have shown a significant increase in the antibody levels at one month, but also the antibody levels decline within the first year after dTap vaccination.[35] Therefore, we do not expect the antibodies from a single dTap administration in pregnancy to be able to protect infants born from subsequent pregnancies. Thus, maternal immunisation is recommended for each pregnancy. Furthermore, protection is not as good if the mother is only vaccinated within two weeks before the delivery.[28] On the other hand, early vaccination starting from 16 weeks of gestation allows more time for the passive transfer and accumulation of antibody in the foetus, so that the infants' antibody levels are higher than those of their mothers when they are born at term.[36] Moreover, preterm infants are also better protected if the mothers are vaccinated at the second trimester of pregnancy.[37, 38] In addition to Australia and New Zealand, which recommend vaccination as early as 20 and 16 weeks of gestation respectively, the National Advisory Committee on Immunisation (NACI) of Canada also support immunisation as early as 13 weeks.[39]

SIDE EFFECTS AND CONTRAINDICATIONS OF PERTUSSIS VACCINATION

Side effects are usually mild and self-limiting, include pain or swelling at the injection site, mild fever, headache, tiredness, nausea, vomiting, diarrhoea, and stomach-ache. Contraindications are also uncommon. Any woman who has experienced (1) serious allergic reaction to any of the vaccine components or following the previous dose of DTaP-IPV vaccine, or (2) encephalopathy or other neurological conditions within seven days following the previous dose of DTaP-IPV vaccine or a pertussis-containing vaccine should not receive the dTap vaccination. Apparently, no other underlying medical conditions are contraindications for pertussis vaccination. Pertussis vaccination is an inactivated vaccine which will not be affected by, nor interfere with, the routine anti-D prophylaxis for Rh-D negative mothers. The administration of dTap should not be delayed due to the mother receiving anti-D. Moreover, seasonal flu vaccination can be co-administered with dTap during the same antenatal visit.

RECOMMENDATIONS OF CHP AND CURRENT PRACTICE IN HA AND MCHC'S

The Scientific Committee on Vaccine-Preventable Diseases of CHP recommends maternal pertussis vaccination in each pregnancy with either dTap or dTap-IPV to be given at any time in the second or third trimester, preferably before 35 weeks of gestation. The Committee also recommends that women who have not received the vaccine during pregnancy would still be benefited by receiving one dose as early as possible after delivery, preferably before discharge from the hospital.

From July 2 2020, both MCHCs of the DH and the antenatal clinics of the HA provide dTap vaccination for all women between 26 and 34 weeks of pregnancy when they attend the antenatal visit. After the initial few months of catch-up period, for those women who have not received antenatal vaccination, postpartum vaccination is not provided before hospital discharge. Meanwhile, maternal seasonal flu vaccination is not covered under the routine antenatal care.

SUMMARY

In summary, maternal pertussis vaccination is a safe and effective intervention to prevent pertussis infection in infants at the window period before neonatal immunisation takes effect. It is now a routine service incorporated into the antenatal care under the DH and HA. Special attention should be paid to women at risk of preterm delivery, and the timing of vaccination should be advanced accordingly. Maternal immunisation has the potential to improve the health of mothers and young infants. The vaccination for COVID-19 is available at the time of writing, but its vaccination in pregnancy remains controversial. Other diseases of relevance are now under research and vaccine development, namely group B streptococcus and respiratory syncytial virus.

DECLARATION ON THE CONFLICT OF INTEREST

Professor Tam was the committee member representing the HKCOG in the Scientific Committee on Vaccine-Preventable Diseases that recommended antenatal pertussis immunisation policy in January 2019. Professor Tam received financial support from GlaxoSmithKline in participating in a regional maternal immunisation advisory board meeting.

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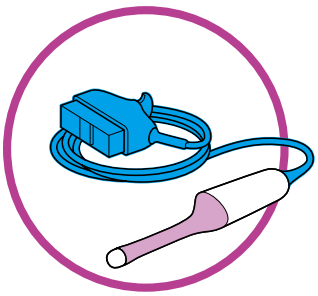

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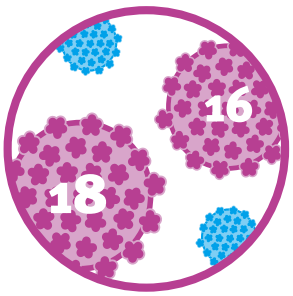

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Use of Oxytocic Agents in the Management of Postpartum Haemorrhage

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Postpartum haemorrhage(PPH) is the major cause of maternal death and morbidity worldwide,[1] commonly due to uterine atony (approximately 70% of cases)[2]. Active management of the third stage of labour involves the use of interventions (including the use of uterotonics, early clamping of the umbilical cord and controlled cord traction) to expedite delivery of the placenta with the aim of reducing blood loss, and has been recommended to be performed routinely by the RCOG[3]. Various uterotonic medications have been used for the prophylaxis and treatment of postpartum haemorrhage across the years, with new ones coming to the market. However, there is still a lack of large studies looking into the cost-effectiveness of different medications. Moreover, numerous studies are comparing different uterotonic medications on different contexts, such as prophylactic and therapeutic (i.e. after the identification of PPH), vaginal deliveries and Caesarean deliveries, elective and intrapartum Caesarean deliveries, low-risk populations and high-risk populations. There are also variations in the outcomes, some studies measuring the total blood loss, others measuring the PPH rate, or the need for additional uterotonic medication or procedures. Hence a "panel of choice" for clinicians when it comes down to the actual choice of medication. This review article presents current choices for uterotonic medications, the guidelines, and the recent updates in research.

CHOICES OF UTEROTONIC MEDICATIONS

Oxytocin

Oxytocin (Syntocinon®) is the most widely used uterotonic agent. It has a short half-life, approximately three to five minutes, and can be used as an infusion to maintain uterine contraction. It is unstable in ambient temperatures, and it requires a cold chain through storage and transport. Used as a prophylactic agent during the third stage of labour, it can reduce the rate of PPH and need for therapeutic agents by 40%.[4] Its main side effects include hypotension if given in a large bolus, and water intoxication if given for a prolonged period.[5]

Ergometrine

Ergometrine is an ergot alkaloid that increases the uterine muscle tone by causing sustained uterine contractions. The half-life is 30 to 120 minutes.[6] The duration of action is 45 minutes, with rhythmic contractions persisting up to three hours. It, therefore, provides a longer uterotonic action. It also requires storage at a temperature between 2 to 8°C, and protection from light. It is vasoconstrictive and is, therefore, contraindicated in women with asthma, hypertensive or cardiovascular disorders. It is commonly combined in a fixed-dose fashion with oxytocin (Syntometrine®) and given in an intramuscular route.[7]

Misoprostol

Misoprostol is a prostaglandin E1 analogue, and is used off-label as a uterotonic agent.[8] It can be given in oral, sublingual, vaginal and rectal route. It is known to have certain side effects, including shivering, fever, and diarrhoea. It is heat stable, with a half-life of 20 to 40 minutes.

Carboprost

Carboprosttromethamine (Hemabate®) is the most commonly used injectable prostaglandin analogue of PGF2a. The half-life is about eight minutes and requires storage at a temperature between 2 to 8°C. The recommended dose is 250 micrograms, repeated every 15 minutes to a total dose of 2 mg (eight doses). It can be administered as an intramuscular or intramyometrial injection. It improves uterine contractility and causes vasoconstriction, but is not contraindicated in hypertensive women. It is, however, contraindicated in patients with active cardiac disease or asthma.

Carbetocin

Carbetocin is a newer synthetic analogue of oxytocin which has a longer half-life than oxytocin, thus reducing the requirement for an infusion after the initial dose. It produces sustained uterine contractions within two minutes after injection, lasting for approximately six minutes, followed by rhythmic contractions for 60 minutes.[9] It is heat stable and does not require refrigeration. It has a similar side effect profile as oxytocin.[10] Its main contraindications include severe cardiovascular disease, epilepsy, and liver and renal impairment. For patients with eclampsia or severe pre-eclampsia, monitoring of changes in blood pressure is required.

PREVENTION OF PRIMARY PPH

The WHO has published her recommendations on the use of uterotonic agents for the prevention of PPH in 2018, and has recommended the use of one and only one

of the following pharmaceutical agents[11]:

- Oxytocin (10 IU, IM/IV)
- Carbetocin (100 micrograms, IM/IV)
- Misoprostol (400 or 600 micrograms, PO)
- Ergometrine/methylergometrine (200 microgram, IM/IV) if no hypertensive disorder
- Syntometrine (5 IU/500 microgram, IM) if no hypertensive disorder

The WHO has made such recommendations based on studies on their efficacy in preventing PPH, reducing blood loss and reducing the need of additional uterotonic agents, when compared to placebo or no uterotonics. However, it did not tell clinicians which one of them should be used.

A Cochrane review[12] in 2018 performed a network meta-analysis of 196 randomised trials to compare the efficacy between different uterotonic agents. Compared to oxytocin alone, the three highest ranked uterotonic agents for PPH > 1,000 ml were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. Nevertheless, the latter is seldom used in Hong Kong.

In local hospitals, ergometrine plus oxytocin combination (syntometrine) is commonly used to prevent PPH if there is no contraindication like hypertension or heart disease. Or else, oxytocin alone will be used. Significant side effects of syntometrine include vomiting, fever and hypertension.

Carbetocin is increasingly used in the public and private sector for the prevention of PPH. A Cochrane review in 2012 addressed that the use of carbetocin resulted in a statistically significant reduction in the need for further uterotonics compared with oxytocin for those undergoing a caesarean section10. A meta-analysis in 2019 involving 30 trials has shown that carbetocin effectively reduces the need for additional uterotonic use and postpartum blood transfusion in women at increased risk of postpartum haemorrhage after Caesarean delivery[13]. Most of these studies were performed on the general population without significant risk factors for PPH. A local study in 2020 compared the efficacy between Carbetocin and oxytocin infusion after Caesarean deliveries, and has shown that there was a significant reduction in the requirement for additional uterotonics or procedures, and in the rate of postpartum haemorrhage for women with major placenta praevia or with multiple pregnancies who received Carbetocin[14]. The use of carbetocin was also associated with a reduction in hysterectomy rate for those with multiple pregnancies.[14] Carbetocin can induce strong contraction of an over distended uterus associated with twin pregnancies. The beneficial effect of carbetocin in reducing bleeding in placenta previa might be related to its effectiveness in stimulating the retroplacental myometrium.[15] The side-effect profiles of Carbetocin is similar to oxytocin, and is more favourable than syntometrine. Although the unit cost for carbetocin is more expensive than oxytocin, carbetocin is more cost-effective than oxytocin in some cost-effectiveness analyses when the reduction of PPH events and secondary uterotonic treatment are considered.[12, 16]

The use of carbetocin has been acknowledged in Canada society[17] and the RCOG guidelines[3]. We suggest using carbetocin in Caesarean deliveries for multiple pregnancies and placenta praevia major type. In women with other risk factors for PPH, we suggest using oxytocin infusion which may have differential effects on the requirement for additional uterotonics or procedures compared to carbetocin[14]. Other than Caesarean deliveries, there are recently more studies investigating its use in vaginal deliveries. One randomised controlled trial has concluded that intravenous injection of 100 ug carbetocin is more effective than 5 u oxytocin to prevent atonic PPH among singleton pregnancies with at least one risk factor for PPH.[18] A recent systematic review and meta-analysis has shown that oxytocin (via injection into the umbilical vein) was inferior to carbetocin in reducing the chance of retained placenta (RR 1.51, 95% CI 1.03-2.52), a known cause of PPH.[19]

TREATMENT OF POSTPARTUM HAEMORRHAGE DUE TO UTERINE ATONY

Most studies have largely looked into the different pharmacological agents to prevent PPH, but not its treatment. There is often confusion between the uterotonic agents to be used once postpartum haemorrhage or uterine atony has been identified. This confusion often leads to an administration of "prophylactic" uterotonic agents in the setting once PPH has been noted.

After the initial uterine massage and urinary catheterisation, several uterotonicagents as well as transamin are indicated before further interventions like balloon tamponade, pelvic embolisation and surgical treatment. The RCOG recommends the use of oxytocic agents including oxytocin 5 unit slow IV bolus, ergometrine 0.5 mg slow IV/IM, oxytocin infusion (40 IU in 500 ml crystalloids at 125 ml/hour), carboprost 0.25 mg IM and misoprostol 800 micrograms for uterine atony.[3] To date, no large studies are comparing all uterotonic agents and their efficacy in treating PPH.

Most clinicians follow the workflow of oxytocin infusion first, then carboprost for two or more doses. Oxytocin infusion is commonly used after delivery in women at high risk of PPH. There is a lack of evidence in the difference in efficacy between carboprost and oxytocin infusion in PPH treatment. Due to side effects of carboprost (nausea, vomiting, diarrhoea), it is usually reserved as the second-line treatment. A Cochrane review in 2014 compared different uterotonic agents in the treatment of PPH. It concluded that compared with misoprostol, oxytocin infusion is more effective and causes fewer side effects when used as first-line therapy for the treatment of primary PPH.[20] Among women who received oxytocin for treatment of primary PPH, adjunctive use of misoprostol confers no added benefit. Moreover, it can take up to 1.0-2.5 hours to increase the uterine tone after administration.[21] Its use has been reducing, especially in countries where there are better alternatives.

Carbetocin has been shown to be an effective medication in the prevention of PPH. Multiple studies have shown

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Abbreviated Prescribing Information of DURATOCIN
Active Ingredient: Carbetocin. **Indications:** Prevention of uterine atony & postpartum haemorrhage following elective caesarean section under epidural or spinal anaesthesia. **Dosage & Administration:** 100 mcg by IV bolus slowly over 1 min, only when delivery of infant has been completed. Can be administered either before or after delivery of the placenta. **Contraindications:** Prior to delivery of the infant for any reasons. Hypersensitivity. Vascular disease esp CAD. Hepatic or renal disease. Not intended for use in childn. Should not be administered prior to delivery of the infant for any reasons eg, elective or medical induction of labour. **Special Warnings and Precautions:** Do not repeat treatment in patient w/ inadequate uterine contraction. Epilepsy, migraine, asthma, any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. Monitor BP in eclampsia & preeclampsia for up to 8 hr. Not recommended in elderly patients. **Side Effects:** Nausea, abdominal pain, pruritus, flushing, vomiting, feeling of warmth, hypotension, headache, tremor. **Interactions:** Concomitant use w/ vasoconstrictors in conjunction w/ caudal block anaesth may lead to HTN; concomitant use w/ cyclopropane anaesthesia may modify cardiovascular effects and lead to hypotension, maternal sinus bradycardia w/ abnormal atrioventricular rhythms.

Reference: Hong Kong Product Package Insert of DURATOCIN (Date of revision: SEP 2015)

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its beneficial effect in reducing the need for additional uterotonics in the setting of Caesarean section. Theoretically, it leads to a more sustained uterine contraction and may be better in the treatment of PPH, when compared to oxytocin. However, to date, there are no large studies to prove its superior efficacy in the setting of treating PPH.

CONCLUSION

Postpartum haemorrhage remains a major health issue globally. Different uterotonic agents have different mechanisms and may have preferential effects in different circumstances. Physicians should be well aware of the current updates and the settings when these uterotonic agents should be used.

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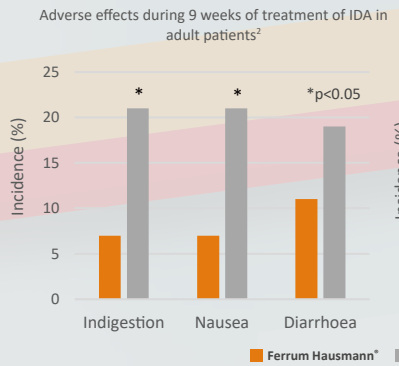

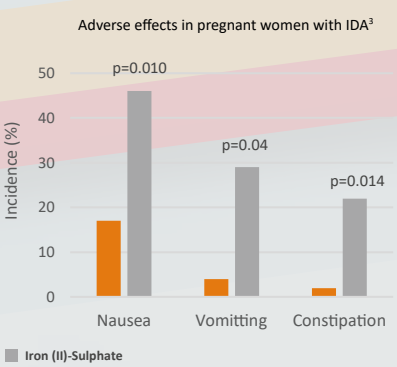

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Answering Some Questions on Telemedicine

Dr Kenneth TSANG
MBBS (HKU) FHKAM (Community Medicine), FHKCCM, FRACMA, MOM (CUHK)

Dr Kenneth TSANG

INTRODUCTION

Virtual consultations have bloomed like wildflowers amidst the COVID-19 pandemic. This is the medical community's answer to the need of the patients who wish to seek medical care but wished to avoid crowdedness in clinics and hospitals. However, we should note that this sort of virtual consultations has been under development in the U.S.A., the UK and Australia for over a decade. It is technically feasible and considered safe in many respects.

However, virtual consultation is only one aspect of telemedicine. Telemedicine, in fact, comprises a broad range of services provided by a medical practitioner. The American Medical Association defines telemedicine as using information technology to provide clinical health care from a distance[1].

In this article, the author wishes to provide some answers to questions raised on different platforms and by different parties.

CAN DOCTORS PRACTISE TEMEMEDICINE IN HONG KONG?

The Government of HKSAR has also anticipated the growth of telemedicine. In the Private Healthcare Facilities Ordinance Cap 633[2] gazetted on 30 November 2018 and the related Code of Practice for Private Hospitals[3] published June 2019, there is already a clear framework on how to practise telemedicine in the hospital. The key areas that must be observed are that the overall standard of care delivered by telemedicine is not compromised as compared with in-person service; staff have the necessary qualification and competence; staff and patient must be able to identify each other. The importance of privacy and security of data and records is also emphasised.

The Medical Council of Hong Kong (MCHK) also published an ethical guideline[4] in December 2019. The MCHK adopted the World Medical Association definition[5] and clearly explained the ethical standpoints. The MCHK recognises that telemedicine is still in the developmental stage in Hong Kong, and therefore, the guidelines aimed to be broad and generic in nature.

In short, doctors can practice telemedicine in Hong Kong.

DOES MEDICAL MALPRACTICE INSURANCE COVER TELEMEDICINE?

The Medical Protection Society (MPS) has specifically provided her members with information on the practice of telemedicine. The MPS held a webinar in April 2020, explaining to members that the MPS supports the use of telemedicine. The MPS has also published, on her website, scenarios[6] where medical practitioners should be mindful of when practising telemedicine. During one of the webinars, specific questions has been raised whether the practice of telemedicine would require an extra premium for malpractice insurance. The MPS has explicitly stated in general circumstances; telemedicine does not warrant extra premium.

IS TELEMEDICINE A NEW SPECIALTY?

This question was recently discussed in the Frontiers in Medical and Health Sciences Education 2020 virtual conference organised by the University of Hong Kong LKS Faculty of Medicine. In the panel discussion on 'What's Beyond Gen Z?' the question on how we should view telemedicine in medical education was raised. The panelists all agreed that telemedicine is a new tool in medicine, as much as robotic surgery arm in surgery and echocardiogram in cardiology.

Telemedicine should enhance doctors' ability and efficiency in managing their patients.

WHAT KIND OF PATIENTS ARE SUITABLE FOR TELEMEDICINE?

Given telemedicine is a new kid in the block, the author is of the opinion that telemedicine can be safely practised on patients in stable conditions or on patients without symptoms that may lead to immediate risks. Patients falling into this category include those with simple episodic diseases and those with chronic diseases for which ongoing monitoring and re-prescription of medication are required.

In overseas countries with more extensive telehealth experience, extensive explorations are being implemented to cater to broad categories of patients. For example, the Australia Ministry of Health is moving towards the virtual hospital to manage rural patients[7].

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IS HONG KONG A SUITABLE PLACE TO IMPLEMENT TELEMEDICINE?

Hong Kong is a compact city, and residents tend to think that it is easy for patients to seek medical care. However, whether medical care is accessible is a perception that is changing. Working-class people no longer wish to wait in queues to see a doctor. Additionally, there is so much that can be done through the internet and mobile phones nowadays that local residents are expecting Hong Kong to follow suit as other countries to provide virtual care.

Hong Kong is in a good position to develop telemedicine because of her sound telecommunication facilities; the unprecedented situation presented by COVID-19 has created an even stronger case for telemedicine in Hong Kong.

Telemedicine improves the access to care, allowing patients to receive health care at any time and from any place. This is particularly important to Hong Kong people who have healthcare needs but may not be able to physically visit a doctor as a result of their busy lives.

In both public and private sectors, we see more and more healthcare institutions adopting telemedicine to ensure continued care to patients in need while minimising the risks for patients and healthcare staff during the pandemic.

To ensure that the teleconsultation can be carried out smoothly, patients are recommended to attend the consultation in a quiet environment and check the functions of device and network connection. If technical and environmental limitations affect the quality of a virtual consultation, the doctor should make the judgement to determine whether the consultation should continue.

WILL TELEMEDICINE PROVIDE AN EASIER WAY FOR GETTING DRUGS OR MEDICAL CERTIFICATES?

Registered medical practitioners in Hong Kong are required to observe the Medical Council's Code of Professional Conduct, which provides guidance on professional conduct and responsibilities including the prescription of medications and issuance of certificates and documents.

We trust that doctors will remain professional when conducting a consultation, giving medical advice and making appropriate judgement, regardless of the mode in which it is delivered.

While teleconsultation can help make provision of health care more efficient and accessible to patients of certain conditions, it does not replace the need for physical consultations entirely.

In fact, in our hospital's experience, the patient's preliminary information would help determine the suitability for teleconsultation before such service is provided. These information are important to ensure that patients will be given the most appropriate care. If a doctor determines that a physical assessment is necessary, the patient will be advised to make a physical visit to the doctor or undergo other assessment such as diagnostic imaging.

WHAT TRAINING DO DOCTORS HAVE TO RECEIVE FOR PERFORMING VIDEO CONSULTATION THROUGH MOBILE?

In addition to getting familiar with how to use the devices and the software, doctors are provided with reminders on the procedures of conducting a video consultation, e.g. checking with the patient on his/her identity card number and place of residence, and advise the patient if he/she should seek alternative medical assistance as appropriate, including in-person consultation, and A&E visit for urgent care.

OTHER UNRESOLVED ISSUES

As MCHK stated, telemedicine is in the developmental stage. Many areas require further deliberation and assessment. Issues such as cross-border consultations, informed consent, and documentation need to be studied. Another contentious issue is how to adhere to the Ordinances related to drug prescription, dispensing and delivery, which is a real challenge.

CONCLUSION

The author would like to conclude this discussion with a real-life situation which challenges you to think of a way to handle. How would you handle a manic patient who is alone in his apartment jumping up and down in front of the camera? The doctor in our hospital was eventually able to calm him down via telemedicine. This personal experience exemplifies how much work there is to do to make telemedicine a useful and safe tool.

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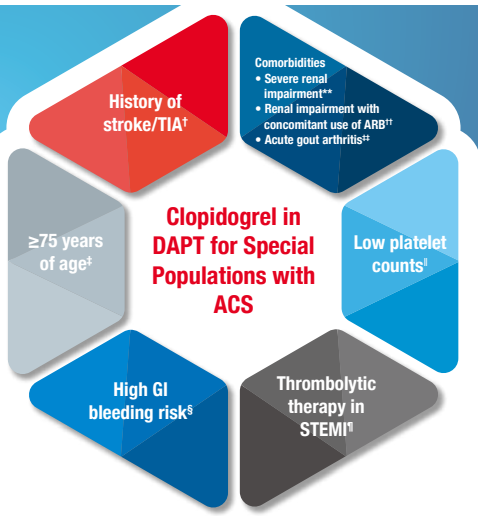

† For ACS patients with a history of ischaemic stroke or TIA, clopidogrel (75 mg/day) plus aspirin (100 mg/day) should be continued to 12 months.

‡ For patients with ACS ≥75 years of age, on top of using aspirin, clopidogrel is recommended as the first-choice P2Y$_{12}$ inhibitor.

§ For ACS patients with a high risk of GI bleeding (including the elderly and patients taking other medications such as warfarin, glucocorticoids or NSAIDs etc.), PPIs for 1-3 months are recommended on the basis of clopidogrel and aspirin.

¶ Patients with STEMI receiving thrombolytic therapy should initiate DAPT as soon as possible. Aspirin is given at a loading dose of 200-300 mg (chew and swallow) followed by 100 mg/day. For patients aged ≤75 years, clopidogrel at a loading dose of 300 mg followed by 75 mg/day should be given; No loading dose is given for patients aged >75 years. Ticagrelor is not recommended for patients with STEMI receiving thrombolytic therapy. In the case of patients undergoing PCI after thrombolytic therapy, taking into account both ischaemic and haemorrhagic risks, administration of ticagrelor can be considered 48 hours after thrombolytic therapy.

‖ If the ACS patient has a low platelet count of <100 x 10^9/L and >60 x 10^9/L, it is needed to carefully assess the safety of DAPT. For patients with low bleeding risk, clopidogrel plus aspirin is preferred. For patients with high bleeding risk, monotherapy (clopidogrel or aspirin) can be considered. The use of ticagrelor should be avoided. If the ACS patient has a platelet count of <60 x 10^9/L and >30 x 10^9/L, it is recommended to use monotherapy (clopidogrel or aspirin) as maintenance treatment. The use of ticagrelor should be avoided. If the ACS patients has a platelet count <30 x 10^9/L, it is recommended to stop antiplatelet therapy and to avoid PCI.

** For ACS patients with severe renal impairment (eGFR <30 mL/min), clopidogrel (75 mg/day) plus aspirin (100 mg/day) is preferred.

†† If a concomitant ARB is given to ACS patients with renal impairment, DAPT of clopidogrel plus aspirin is preferred.

‡‡ For ACS patients with comorbid acute gout arthritis flares, clopidogrel at 75-150 mg/day is preferred. Once symptoms are relieved, initiate clopidogrel at 75 mg/day plus aspirin at 75-100 mg/day. After 6-12 months, maintain with clopidogrel at 75 mg/day for long-term treatment. In case of acute gout during administration of DAPT following PCI, concomitant use of antigout agents with DAPT of clopidogrel plus aspirin can be considered taking into account of the risks for ischaemia and gout. Low-dose aspirin (75-325 mg/day) has a mild effect on increasing plasma uric acid, which raises the risk of gout. If the risk of gout has been increased by aspirin, stop using aspirin or replace with cilostazol plus clopidogrel.

ACS=acute coronary syndrome. ARB=angiotensin II receptor blocker. CHD=coronary heart disease. DAPT=dual antiplatelet therapy. eGFR=estimated glomerular filtration rate. GI=gastrointestinal. NOAC=novel oral anticoagulant. NSAID=non-steroidal anti-inflammatory drug. PCI=percutaneous coronary intervention. PPI=proton pump inhibitor. PTE=pulmonary thromboembolism. STEMI=ST-elevation myocardial infarction. TIA=temporary ischaemic attack.

Reference

Specialty Committee on Prevention and Treatment of Thrombosis of Chinese College of Cardiovascular Physicians, Interventional Cardiology Branch of Chinese Society of Cardiology of Chinese Medical Association and Editorial Board of Chinese Journal of Cardiology. Chinese expert consensus on antiplatelet therapy for special patients with acute coronary syndrome. Chin J Cardiol 2018;46:255-266.

Presentation: Clopidogrel film-coated tablets. **Indications:** Prevention of atherothrombotic events in (a) adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) & established peripheral arterial disease (b) adult patients suffering from acute coronary syndrome: (i) Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA) (ii) ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy. Prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk. **Dosage:** Adults and elderly: 75mg once daily. For patients with UA/NQWMI, loading dose 300mg, followed by 75mg once daily (with ASA 75mg-325mg daily). Since higher doses of ASA were associated with higher bleeding risk, recommended dose of ASA ≤100 mg. For patients with ST segment elevation myocardial infarction, 75mg once daily with a 300mg loading dose in combination with ASA and with or without thrombolytics. For patients ≥75 years, initiate clopidogrel without loading dose. For patients with atrial fibrillation, 75 mg daily with ASA (75-100 mg daily). Children and adolescents: not recommended under 18 years. **Contraindications:** Hypersensitivity to clopidogrel or excipients; severe hepatic impairment; active pathological bleeding such as peptic ulcer & intracranial haemorrhage. **Precautions:** If a patient is to undergo elective surgery and antiplatelet effect is not necessary, clopidogrel should be discontinued 7 days prior to surgery. Patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions; hypersensitivity to thienopyridines; patients with renal impairment; patients with moderate hepatic disease who may have bleeding diatheses. Not recommended during the first 7 days after an acute ischaemic stroke. Patients with genetically reduced CYP2C19 function. Patients treated concomitantly with clopidogrel and CYP2C8 substrates. **Interactions:** Not recommended with oral anticoagulants, caution with glycoprotein IIb/IIIa inhibitors, aspirin, heparin, thrombolytics or NSAIDs (including Cox-2 inhibitors), selective serotonin reuptake inhibitors (SSRIs). Drugs that inhibit CYP2C19, including proton pump inhibitors. CYP2C8 substrates such as rapaglinide and paclitaxel. **Undesirable effects:** haemorrhagic disorders; haematological including bleeding such as purpura, bruising, haematoma and epistaxis; gastrointestinal system disorders such as dyspepsia, abdominal pain and diarrhea. For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information. **Preparations:** 75 mg x 14's; 300 mg x 30's. **Legal Classification:** Part 1, First & Third Schedules Poison ***Full prescribing information is available upon request.*** API-HK-CLO-18.04

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7	8	* Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures) 9	* The Hong Kong Neurosurgical Society Monthly Academic Meeting - Neuro-rehabilitation * Facebook Live Multidisciplinary Management of LUTS Patients - Online * Certificate Course in Ophthalmology 2021(Video Lectures) 10	* Facebook Live Early Rhythm-Control Therapy in Patients with Atrial Fibrillation - Online 11	* Facebook Live HKMA-GHK CME Programme Topic: Update on Minimally invasive spine surgery (Online Lecture) 12	13
14	15	* Facebook Live Right Treatment at the Right time for the Men with BPH / LUTS - Online * Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures) 16	* Certificate Course in Ophthalmology 2021(Video Lectures) 17	* FMSHK Executive Committee Meeting 18	19	20
21	22	* Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures) 23	* Facebook Live Choosing Right Beta-blocker for CHF and HTN - Online * Certificate Course in Ophthalmology 2021(Video Lectures) 24	* Facebook Live Evolution of Thyroidectomy in the Era of Technology - Online 25	* Facebook Live Importance of Controlling Allergic Rhinitis in Children During Pandemic - Online 26	27
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7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Roanna YEUNG	Ms Vienna LAM Tel: 2527 8898
3 WED 7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Bonnie Nga-kwan CHOY, Dr Jasper Ka-wai WONG	Ms Vienna LAM Tel: 2527 8898
2:00 PM	**Facebook Live** **The evolving landscape of anticoagulation management in Atrial Fibrillation - Online** Organiser: Hong Kong Medical Association; Speaker: Dr JIM Man-hong	HKMA CME Dept. 3108 2507 1 CME Point
9 TUE 7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Assunta HO, Dr Andrea LEUNG	Ms Vienna LAM Tel: 2527 8898
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting - Neuro-rehabilitation** Organiser: Hong Kong Neurosurgical Society Speaker: Dr CHEUNG Ling-kit Chairman: Dr POON Tak-lap Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
2:00 PM	**Facebook Live** **Multidisciplinary Management of LUTS Patients - Online** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr Charles Fei CHAN	Miss Antonia LEE 3108 2514 1 CME Point
7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr HO Wing-lau, Jason Cheuk-sing YAM	Ms Vienna LAM Tel: 2527 8898
11 THU 2:00 PM	**Facebook Live** **Early Rhythm-Control Therapy in Patients with Atrial Fibrillation - Online** Organiser: HKMA-KLN East Community Network; Speaker: Dr HUNG Yu-tak	Miss Antonia LEE 3108 2514 1 CME Point
12 FRI 2:00 PM	**Facebook Live** **HKMA-GHK CME Programme** **Topic: Update on Minimally invasive spine surgery (Online Lecture)** Organiser: Hong Kong Medical Association Gleneagles Hong Kong Hospital; Speaker: Dr Eric Cheung-hing LAM	HKMA CME Department 2527 8452 1 CME Point
16 TUE 2:00 PM	**Facebook Live** **Right Treatment at the Right time for the Men with BPH / LUTS - Online** Organiser: HKMA-YTM Community Network; Speaker: Dr LEUNG Yiu-lam	Ms. Candice TONG 3108 2513 1 CME Point
7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr David LUK	Ms Vienna LAM Tel: 2527 8898
17 WED 7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Jeremy John Sze-wai KWOK. Dr Allie LEE	Ms Vienna LAM Tel: 2527 8898
18 THU 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
23 TUE 7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Grace CHIANG	Ms Vienna LAM Tel: 2527 8898
24 WED 2:00 PM	**Facebook Live** **Choosing Right Beta-blocker for CHF and HTN - Online** Organiser: Hong Kong Medical Association; Speaker: Dr Danny Hoi-fan CHOW	HKMA CME Department 2527 8452 1 CME Point
7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Fiona Oi-jing LUK, Dr Frank Hiu-ping LAI	Ms Vienna LAM Tel: 2527 8898
25 THU 2:00 PM	**Facebook Live** **Evolution of Thyroidectomy in the Era of Technology - Online** Organiser: HKMA Hong Kong East Community Network; Speaker: Dr WONG Kai-pun	Ms. Candice TONG 3108 2513 1 CME Point
26 FRI 2:00 PM	**Facebook Live** **Importance of Controlling Allergic Rhinitis in Children During Pandemic - Online** Organiser: HKMA-KLN City Community Network; Speaker: Dr TSANG Wing-yan	Ms. Candice TONG 3108 2513 1 CME Point
30 TUE 7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Celeste EWIG	Ms Vienna LAM Tel: 2527 8898
31 WED 7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr MOHAMED Shaheeda, Dr Joy Wing-yun SEE LEUNG	Ms Vienna LAM Tel: 2527 8898

Answers to Dermatology Quiz

Answers:

1. The possible differential diagnoses include small epidermoid cyst, syringoma, steatocystoma, calcinosis cutis and gouty tophus. An epidermoid cyst is a flesh coloured or yellowish papule characterised by a central punctum. Syringoma and steatocystoma are uncommon on the pinna. Gouty tophus is commonly found on joints and pinna.

2. It is difficult to differentiate among these diagnoses based on the clinical examination. Hence, a skin biopsy is needed to reach a definitive diagnosis. The biopsy report showed pale eosinophilic fibrillary material surrounded by histiocytes and foreign body giant cells suggestive of gouty tophi. Although polarised light is not used, the histological picture is still compatible with gouty tophus. The urate crystals might have been dissolved in formalin during the process of Haematoxylin and Eosin (H&E) staining. Absolute alcohol fixation can usually preserve the urate crystals much better.

3. Gout is a common disorder and is caused by excess uric acid, which is mainly from high-protein diets. Blood for urate level may be elevated, and skin biopsy may be needed to differentiate from other causes of yellowish cutaneous papules because the blood urate level may be normal or even low in some patients. NSAIDs, colchicine and oral steroid may be necessary for the acute attack. Allopurinol, probenecid and new medications such as febuxostat and benzbromarone are urate-reducing agents used in cases of chronic hyperuricemia cases. Last but not least, low-purine-diet is the mainstay of treatment.

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

Betmiga®
mirabegron

THE 1ST β_3-AGONIST FOR OAB* PATIENTS
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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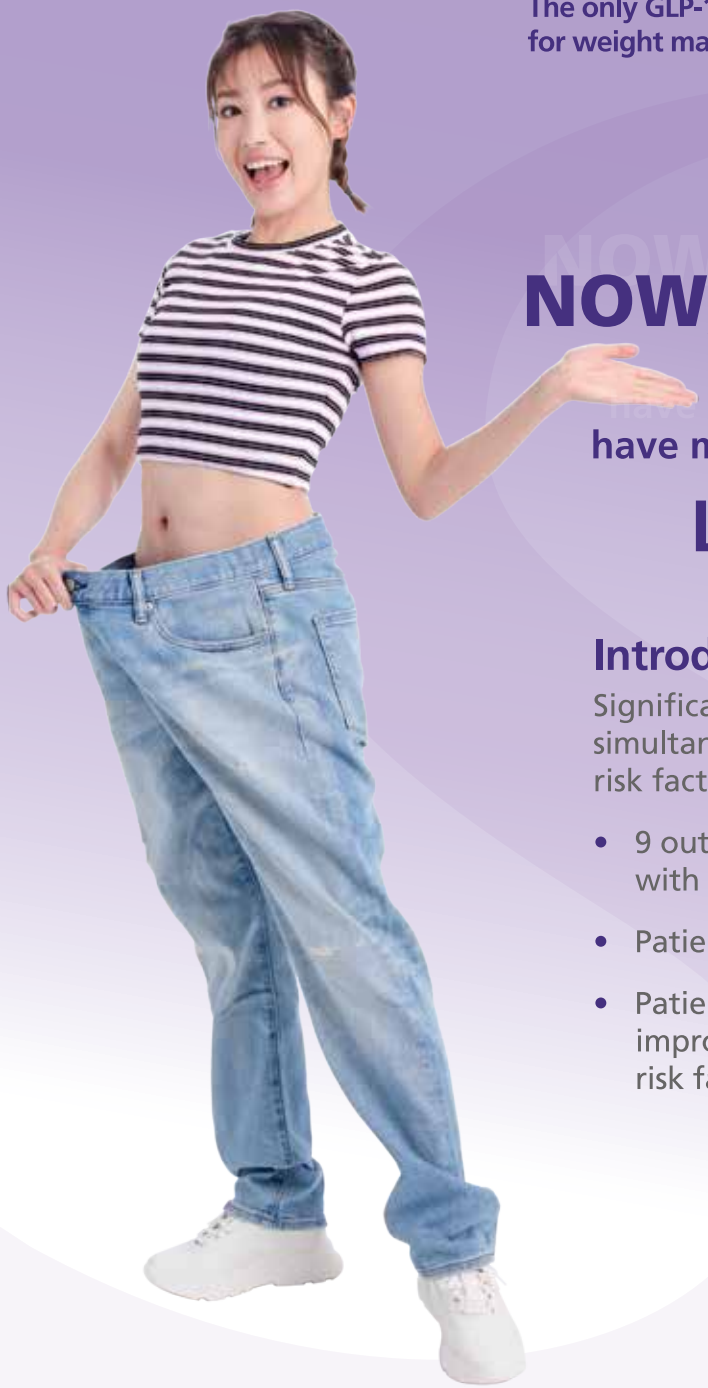
The only GLP-1 analogue that is EMA and U.S. FDA approved for weight management as an adjunct to diet and exercise[1,2]



NOW,

your patients WITH OBESITY have more to celebrate with LOSING WEIGHT

Introducing Saxenda®:

Significant and sustained weight loss with simultaneous improvements in cardiometabolic risk factors.[1,3] In a 1-year study:

- 9 out of 10 patients achieved weight loss, with 1 in 3 losing >10%[3]
- Patients lost weight and kept it off[1]
- Patients also experienced significant improvements in multiple cardiometabolic risk factors[1]

Abbreviated prescribing information

Saxenda® (liraglutide injection) The Summary of Product Characteristics (SPC) is available at novonordisk.com. Presentation: Prefilled, disposable pen containing 18 mg of liraglutide in 3 mL of solution. Indications: Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea. Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight. The need for continued treatment should be re-evaluated annually. **Dosage and administration:** The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least one week interval to improve gastro-intestinal tolerability. If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended. Saxenda® is administered once daily at any time, independent of meals, subcutaneously injected in the abdomen, thigh or upper arm, preferably around the same time every day. Saxenda® must not be administered intravenously or intramuscularly. Patients with type 2 diabetes mellitus receiving liraglutide in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea. Saxenda® should not be used in combination with other Glucagon-like Peptide-1 (GLP-1) receptor agonist. The addition of Saxenda® in patients with type 2 diabetes mellitus treated with insulin has not been evaluated, This medicinal product is not recommended for use in paediatric patients. **Contraindications:** Hypersensitivity to liraglutide or to any of the excipients. **Special warnings and precautions:** In patients with diabetes mellitus liraglutide must not be used as a substitute for insulin. There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and liraglutide should therefore be used with caution. There is no experience in patients with congestive heart failure NYHA class III-IV and liraglutide is therefore not recommended in these patients. Due to limited experience, Saxenda® is not recommended in patients with inflammatory bowel disease or diabetic gastroparesis. Saxenda® is not recommended in patients: aged 75 years or more, treated with other products for weight management, with obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain, with severe renal impairment, with severe hepatic impairment. Saxenda® must be used with caution in patients with mild or moderate hepatic impairment. Use of GLP-1 receptor agonists has been associated with the risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis. In clinical trials in type 2 diabetes, thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in particular in patients with pre-existing thyroid disease. Cases of increased blood calcitonin were also observed in the weight management clinical trials. An increase in heart rate was observed with liraglutide in clinical trials. Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should be informed of the symptoms of increased heart rate (palpitations or feelings of a racing heartbeat while at rest). For patients who experience a clinically relevant sustained increase in resting heart rate, treatment with liraglutide should be discontinued. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. **Pregnancy and lactation:** Saxenda® should not be used in women who are pregnant, who wish to become pregnant, or who are breastfeeding. **Undesirable effects:** The most frequently reported adverse reactions in patients treated with Saxenda® are nausea, vomiting, diarrhoea and constipation. Less common adverse reactions include dyspepsia, upper abdominal pain, gastritis, flatulence, abdominal distension, gastroesophageal reflux, eructation, dry mouth, dizziness, dysgeusia, insomnia, fatigue, asthenia, injection site reactions, malaise, tachycardia, urticaria, pancreatitis, cholelithiasis, cholecystitis, hypoglycaemia, anaphylactic reaction, dehydration, acute renal failure and renal impairment. **Overdose:** From clinical trials and marketed use overdoses have been reported up to 72 mg (24 times the recommended maintenance dose). Events reported included severe nausea and severe vomiting which are also the expected symptoms of an overdose with liraglutide. None of the reports included severe hypoglycaemia. All patients recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

References: 1. Saxenda® [summary of product characteristics]. **2.** NovoNordisk Company press release, 22 Apr 2015. United States first country to launch Saxenda®. **3.** Pi-Sunyer X, Astrup A, Fujioka K, et al; for the SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.

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Saxenda®
Liraglutide injection

SAX-D-20210201