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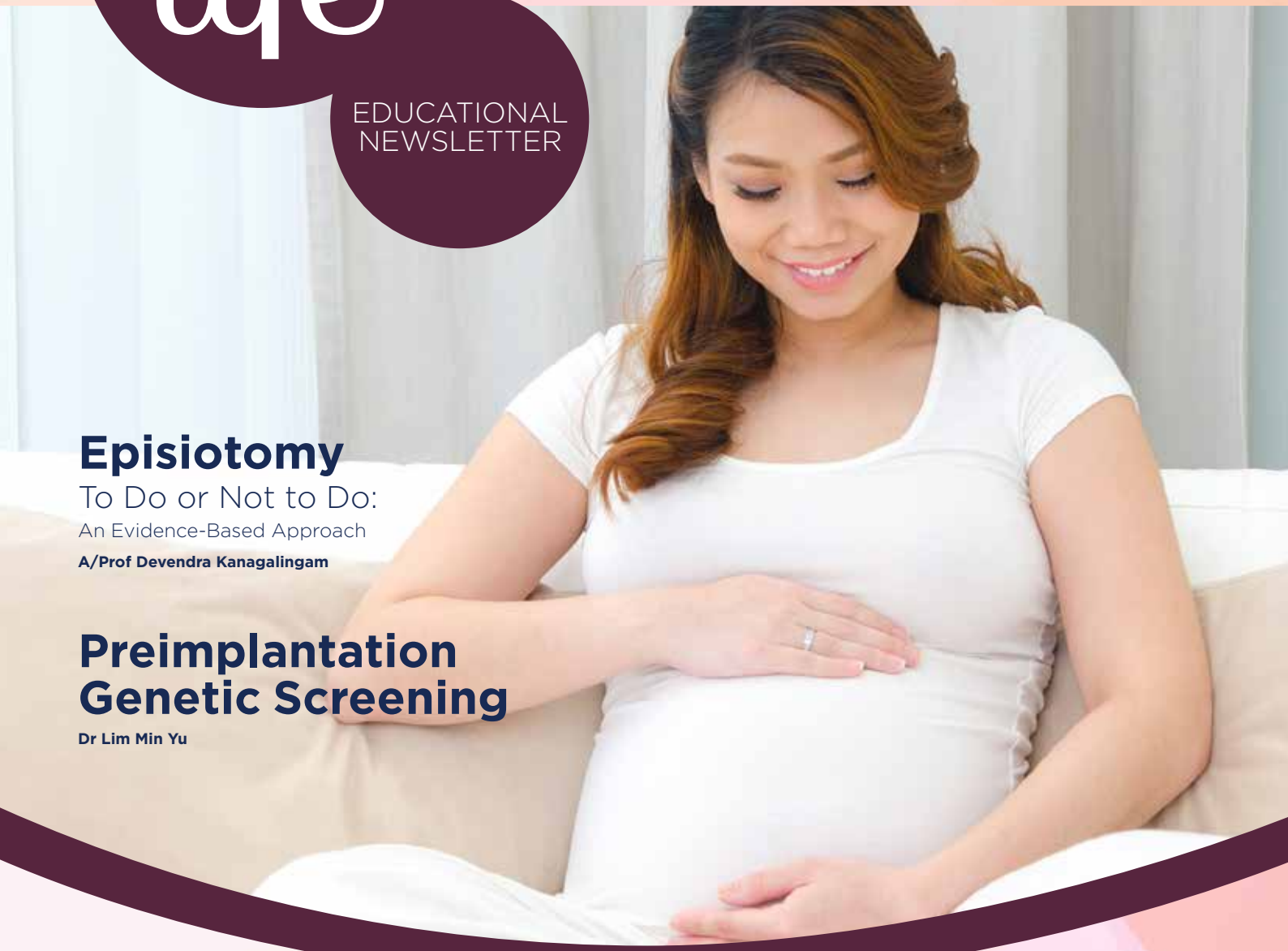

Episiotomy

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An Evidence-Based Approach

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Contents provided by The Obstetrical & Gynecological Society of Singapore (OGSS)

Vol 02: **January 2018**

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DEAR FRIENDS,

Life connects us in many ways, and I did not expect that I would be working closely with you and getting to know each other better before these 4 years in Singapore.

Your participation did not only support the business, but I have found some great friends and mentors among you.

As we kick start the new year, I wish to extend my big thank you for your kind support to our endeavours.

The last year was a tremendous success for establishing our foundation in the Singapore market. We set up our own laboratory in the central part of Singapore, and also took over a few major accounts to extend our services to more clients.

We have been supporting the academia and shall continue to do so as our commitment to medical fraternity.

I wish you a very happy and prosperous new year ahead.

Warm regards,

Dr. Ashish Munjal
Director & CEO
Cryoviva Singapore

EPISIOTOMY: TO DO OR NOT TO DO

AN EVIDENCE-BASED APPROACH

A/Prof Devendra Kanagalingam

Few interventions are as misunderstood or as maligned as the episiotomy. This simple incision to enlarge the vaginal introitus has proponents as well as opponents. The practice was born out of seemingly logical justifications. When I was a medical student, we were told that a linear surgical incision is easier to repair than a spontaneous vaginal tear which may be jagged and haphazard. We were also told that because an episiotomy could be angled away from the anus, it may be helpful in preventing obstetric anal sphincter injuries (OASIS), namely 3rd and 4th degree perineal injuries. Other justifications for episiotomy are hastening delivery when clinically necessary, protection of the fetal head and even reducing damage to the maternal pelvic floor. There is a common perception that the perineum in the Asian woman is intrinsically different and that episiotomy is more likely to be necessary, particularly in primigravidae. There is little scientific evidence to support this belief.

The advent of evidence-based medicine allowed us to put these beliefs and theories to the test. Two approaches to performing an episiotomy have been extensively studied. The first is a liberal approach where there is a low threshold to performing one. The second is restrictive use, where the obstetrician attempts to avoid an episiotomy where possible but will perform one based on clinical judgement in certain scenarios. These two approaches were put to the test. Findings in randomised controlled trials as well as systematic review and meta analysis of these trials (as in the Cochrane Library) support the view that in spontaneous vaginal births, restrictive use was beneficial. A restrictive approach resulted in a lower incidence of severe perineal injury defined as 3rd and 4th degree perineal tears. The irony of this finding must not be lost amongst obstetricians because it means that episiotomies increase the risk of a complication they were designed to prevent. It is explained by the fact that if the perineum is allowed to stretch and tear spontaneously, it should only tear as much as will be necessary to deliver the baby whereas in making an episiotomy, an obstetrician may create a more generous incision than required. Episiotomies have also not been shown to have any fetal benefit in terms of protection to the fetal head or to protect the maternal pelvic floor. A restrictive approach to episiotomy also results in a reduced need for suturing which simply means some women may have intact perineums or very superficial tears which do not require suturing.

The only benefit of a liberal approach appears to be reduced anterior trauma in the perineum. This refers to tears and lacerations in the peri-urethral area and anterior vaginal wall. This finding is explained by the fact that making an incision In the posterior vaginal wall will reduce the pressure and consequent trauma to the opposite anterior vaginal wall. It is also evident that making an episiotomy will hasten delivery of a fetal head which is about to crown so the intervention can be useful in scenarios where fetal distress occurs just prior to crowning. An episiotomy may also be useful to gain access to the vagina to perform the necessary fetal manoeuvres to dislodge the anterior shoulder once shoulder dystocia has been diagnosed.

Be aware that research has focused on comparing a restrictive approach versus a liberal approach and not performing an episiotomy versus not performing one. It is clear that a restrictive approach to episiotomy is beneficial in spontaneous vaginal births but this approach does not mean one should avoid an episiotomy at all costs. A considered approach is called for where an obstetrician allows the perineum to distend and stretch spontaneously and makes a judgment as to whether an episiotomy is needed just before crowning. Clinical information such as fetal head position and fetal size can also be incorporated in this decision-making process and the clinician can choose to perform an episiotomy when there is malposition, such as occiput posterior position when the presenting diameters are larger, of if the fetus is judged to be big. A restrictive approach is, therefore, a matter of subjective assessment and clinical experience. It is unclear what the precise episiotomy rate should be when practicing a restrictive approach and this may differ depending on the patient population. One large randomised controlled trial performed in Argentina suggested that an episiotomy rate of more than 30% was unlikely to be beneficial and this trial was performed in a population where the existing episiotomy rates were high. The role

of episiotomy in operative vaginal deliveries such as vacuum or forceps-assisted deliveries is less clear from the evidence-based perspective and it would seem reasonable to perform an episiotomy in these deliveries, particularly if the forceps is used.

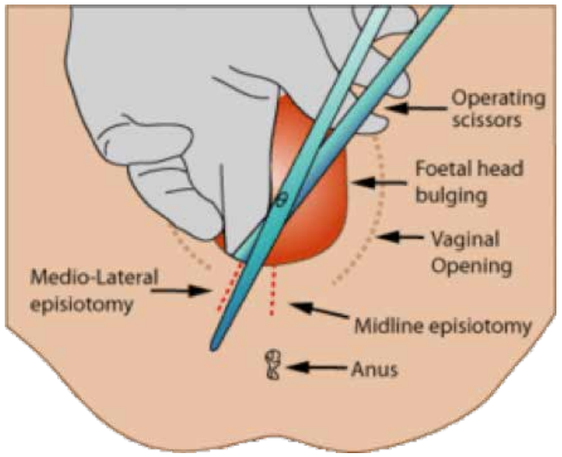

Fig.1 Midline and mediolateral episiotomies

The technique for making an episiotomy has also been studied. Some obstetricians favour a mediolateral episiotomy which is angled between 45 to 60 degrees away from the midline hence directing it away from the anus.

The alternative is a midline episiotomy. Again, I recall having to remember consultants' individual preferences as a trainee because we would be expected to perform these according to instruction if we had to deliver their patients. The evidence is clear on this issue because midline episiotomies have been shown to increase the risk of 3rd and 4th degree tears. Proponents of the midline episiotomy maintain that it is easier to repair, is less painful and even looks nice once repaired. I would suggest that preventing 3rd and 4th degree tears is a far more worthy cause than making stitching easier or reducing short term pain. I also reassure patients that the perineum heals very well regardless of the type of episiotomy and that part of the anatomy is less likely to be matter of public scrutiny anyway!

There is compelling evidence to show that continuous suturing of the episiotomy wound with subcuticular suturing for the skin is associated with less short term pain compared to placing interrupted sutures and wound dehiscence rates are the same with both techniques. Using polyglycolic acid suture materials (such as Vivryl®) is also associated with reduced short-term pain compared to catgut.

TAKE HOME MESSAGES

1. A restrictive approach to episiotomy is shown to be beneficial when compared to liberal/routine episiotomy in spontaneous vaginal births.
2. Episiotomy should be considered when there is a need to expedite delivery, in operative vaginal deliveries and in the management of shoulder dystocia.
3. Mediolateral episiotomies reduce the risk of anal sphincter injuries compared to midline episiotomies.
4. Continuous, subcuticular suturing of an episiotomy wound with polyglycolic acid sutures (Vicryl®) is associated with less short-term pain when compared to interrupted sutures using catgut.

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HAPLOIDENTIAL TRANSPLANTS

Dr Toh Keng Kiat
Director, Medical Affairs, Cryoviva Singapore

Transplantation with stem cells may be syngeneic, autologous or allogeneic. In syngeneic transplants, the donor stem cells are harvested from an identical twin who shares the same genetic composition as the recipient. Autologous transplants are carried out with stem cells derived from the patient (recipient) himself/herself. Matching of the HLA (Human Leucocyte Antigens) is not a concern in both. HLA antigens are protein markers present on all cells which enable the immune system to tell the differences between our own cells and foreign cells.

Allogeneic transplants which are carried out with a HLA matched sibling or matched unrelated donor, however, presents a different situation. In this form of transplantation, a close match of the HLA antigen markers is essential for treatment success.

The closer the match, the more successful the engraftment and reestablishment of marrow function in the patient. Discrepancies or mismatches can lead to failures and a complication known as GVHD (graft versus host disease). The search for a fully HLA matched sibling or unrelated donor can be tedious and time consuming resulting in prognosis becoming adversely affected.

A procedure developed and investigated by doctor-scientists at the Kimmel Cancer

Obstetrical & Gynaecological Society of Singapore

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Centre in John Hopkins Hospital using a non myeloablative priming regime and donor cells that are half HLA matched (haploidentical) or umbilical cord blood cells has shown promising results.

In this procedure, just enough chemotherapy to knock out the recipient's bone marrow is given. This non ablative priming results in suppressing the recipient's immune system so that it will not reject the donor transplanted cells but does not cause damage to other organs. The re-established immune system from the donor stem cells will react more strongly against the cancer cells and prevent a relapse.

On 6 July 2011, John Hopkins Hospital announced promising results from studies on clinical trials on leukaemia/lymphoma patients. Using this technique (non myeloablative) and half HLA matched (haploidentitcal) bone marrow stem cells or umblical cord blood (UCB) cells. The results from these studies from 27 centres on the 50 leukaemia/lymphomas patients were 1 year survival 62% (haplo) and 54% (UCB). 1 year survival with no progression was 48% (haplo) and 46% (UCB). Relapse after 1 year was 45% (haplo) and 31% (UCB).

These investigators were of the view that the results are comparable to the survival achieved for similar patients using fully HLA matched sibling or unrelated adult donors.

Haploidentical (half HLA matched) or umbilical cord blood stem cells has increased the scope of transplant therapy, together with innovative immune procedure.

PREIMPLANTATION GENETIC SCREENING

Dr Lim Min Yu

INTRODUCTION

Singapore's present total fertility rate of 1.20 is well below the population replacement rate of 2.1. Increasing birth rates is a national priority. One of the governmental incentives that has been introduced to improve birth rates is co-funding for assisted reproduction. However, on average, two-thirds of in-vitro fertilisation (IVF) cycles will not be successful. Although there are multiple factors behind unsuccessful IVF, the single biggest impact is thought to be from chromosomal abnormality. The risk of chromosome aneuploidy increases with maternal age, as the oocytes are older and therefore more prone to meiotic disorders. More than half of the embryos from women under age 35 are chromosomally abnormal, rising to over 80% in those above the age of 40 (Ata et al 2012). Transferring an aneuploid embryo may result in failure to implant, miscarriage, or birth with disabilities that can be profound. The conventional method of selecting the best embryo for transfer is based on morphology, that is, their form and structure at defined stages, usually on Day 2, 3 or 5 after fertilization. However, there is poor correlation between morphology, embryo development and having the correct number of chromosomes (Fragouli et al 2014). Morphological assessment of embryos cannot be relied on to ensure transfer of chromosomally normal embryos. Hence there is interest in finding better methods of embryo selection.

Preimplantation genetic screening (PGS) is a technique of selecting embryos for transfer. After IVF, an embryo biopsy is performed, and the biopsied cells analysed for their chromosome content. Only embryos that are euploid, i.e. contain the correct number of chromosomes, are selected for transfer. Earlier attempts to perform PGS using fluorescence in-situ hybridization (FISH) technology were not shown to be beneficial. A maximum of 15 chromosomes could be analysed, therefore the aneuploidy status of the unanalysed chromosomes was unknown. Around 2010, a microarray-based technology that analyses all 24 chromosomes called array comparative genomic hybridization (aCGH) was introduced as an alternative to FISH for PGS (Harper et al 2010). aCGH is associated with relatively high test costs due to the nature of the one cell/ sample per microarray format. More recently, rapid developments in next generation sequencing (NGS) technology have tremendously reduced the cost of sequencing-based genomic analysis (Fiorentino et al 2014). NGS platforms allow multiple samples to be analysed simultaneously. This leads to improved workflow, higher throughput, and lower test costs.

POTENTIAL BENEFITS

PGS could significantly increase overall IVF embryo implantation, clinical pregnancy, and healthy live-birth rates across most if not all prognostic groups. This may in turn translate into fewer IVF cycles that women have to undergo in order to bring home a healthy baby. This will reduce medical costs, physical pain, psychological and mental stress for the patient and family. In the long term, PGS has the potential to reduce the number of IVF treatments needed to produce a healthy baby, to reduce the risk of miscarriage, and to avoid babies born with chromosomal aneuploidy syndromes, translating into a significant reduction in Singapore's overall healthcare burden.

THE EVIDENCE

Three randomised controlled trials of comprehensive chromosome screening had

shown improvements in outcomes. (Yang et al 2012; Forman et al 2013; Scott et al 2013). More recently though, a multicentre randomised controlled trial (Munne et al 2017) of 588 women aged 25 to 40 years found that PGS did not show benefit for all patients. There was, however, an improvement in ongoing pregnancy rate in women above the age of 35 who had PGS (50.8%) versus women who did not (37.2%). The authors of the study suggest that standardization of clinical and laboratory protocols is essential for future studies, as there were 34 clinical sites and 9 laboratories across 4 countries performing the PGS analysis.

CONTROVERSIES

Mosaicism is a phenomenon whereby the chromosome content of different cells varies. Presently, most embryo biopsies are performed at the blastocyst stage. About 5-10 cells from the trophectoderm (which eventually develops into the placenta) are removed and sent for analysis. Using NGS techniques, mosaicism may be detected. Although some practitioners may choose not to recommend transfer of embryos with a mosaic karyotype, others have reported successful live birth with normal chromosome content following transfer of mosaic embryos. However, the pregnancy and live birth rates following transfer of mosaic embryos is lower than following transfer of euploid embryos (Fragouli et al 2017). As this is an evolving situation, more research is required.

PGS IN SINGAPORE

PGS has not been permitted in Singapore by the authorities. However, the Ministry of Health has approved a study that is now underway at the ART centres in the public healthcare institutions. The study is exploring whether PGS using NGS techniques can improve live birth rates in women of advanced maternal age, or in those with recurrent implantation failure, or those with recurrent pregnancy loss. Patient recruitment began in September 2017, and the outcome of this study will be eagerly awaited.

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VACCINATION IN PREGNANCY

Dr Serene Thain

The Ministry of Health (Singapore) has recently extended the use of Medisave for Vaccines under the National Adult Immunisation Schedule (NAIS). From 1st November 2017, Singaporeans can use their Medisave for NAIS vaccinations at Medisave-accredited healthcare institutions, such as hospitals, polyclinics, and CHAS GP clinics. Influenza as well as tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines are covered under this schedule and are recommended for administration in pregnancy. The benefits of antenatal vaccination for influenza and pertussis will be covered in this article.

INFLUENZA VACCINATION IN PREGNANCY

Introduction

Influenza is a highly infectious respiratory viral illness that is transmitted person to person through respiratory droplets propelled by coughing and sneezing or via contact with contaminated surfaces. The contagious period is from 1 day before onset of symptoms till 5 to 7 days after onset. Common symptoms include fever, headache, chills, cough, sore throat, muscle aches and generalized malaise and fatigue.

Locally in Singapore, influenza is commonly seen, with between 1500 and 3500 people experiencing influenza-like illness every week. Most infected people will recover within 1 to 2 weeks, but certain populations such as pregnant women at any stage of pregnancy are at higher risk of morbidity.

Impact of influenza on the pregnant woman compared to the general population

- More likely to develop severe illness
- More likely to be hospitalized
- More likely to be admitted to an intensive care unit
- More likely to die

Impact of influenza on the fetus

- Potential increased risk of congenital abnormalities for influenza or influenza-related illness in the first trimester
- Effect of maternal hyperthermia as a result of influenza illness may increase the risk of certain birth defects
- Reports of increased risk of obstetric complications such as spontaneous abortion, preterm delivery, low birth weight and fetal death

Impact of influenza on the neonate

- Infants less than 6 months old who experience influenza virus infection have the highest rates of hospitalization and death of all children

Benefits of antenatal influenza vaccination

- Reduces risk of serious maternal medical complications
- Provides passive protection to the neonate via trans-placental transmission of antibodies (especially since influenza vaccine is not approved for infants less than 6 months old)

Information on the inactivated influenza vaccine

- The inactivated influenza vaccine is safe in all trimesters of pregnancy, with studies conducted by the Centre for Disease Control and Prevention (CDC) showing no evidence of a link between pregnancy complications or adverse fetal outcomes.
- The vaccine is administered as a single dose repeated yearly with the updated vaccine.
- Common side effects experienced after influenza vaccination include soreness, redness or swelling from the shot, fainting, headache, fever, muscle aches, nausea and fatigue. If these side effects occur, they usually begin soon after the shot is administered and can last for about 1 to 2 days.
- Rarely, influenza vaccines can cause serious problems such as severe allergic reactions. People who have had a severe allergic reaction (e.g. analphylaxis) after a previous dose or a severe allergy to any of the vaccine components should abstain from getting the vaccine.

CURRENT INTERNATIONAL GUIDELINE RECOMMENDATIONS

UK (Public Health England)	Inactivated influenza vaccine should be offered to pregnant women at any stage of pregnancy (1st, 2nd or 3rd trimesters), ideally before influenza viruses start to circulate.
CDC Advisory Committee on Immunization Practices and American College of O&G (ACOG)	All women who are pregnant or will be pregnant during influenza season should receive inactivated influenza vaccine, regardless of trimester.
Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	Influenza vaccination is recommended for all pregnant women regardless of gestation and for women planning pregnancy. Vaccination early in the season and regardless of gestational age is optimal, but unvaccinated pregnant women should be immunized at any time during influenza season as long as the vaccine supply lasts.
Society of Obstetricians and Gynaecologists of Canada (SOGC)	Pregnant women should be offered the influenza vaccine when pregnant during the influenza season.

CURRENT LOCAL GUIDELINE RECOMMENDATIONS

Clinical Practice Guidelines on Adult Vaccination (April 2016)	Routine influenza (inactivated) vaccine for pregnant women is strongly recommended.
Ministry of Health (Singapore) National Adult Immunisation Schedule (NAIS)	Women at all stages of pregnancy should receive 1 dose of influenza vaccine annually.

PERTUSSIS VACCINATION IN PREGNANCY

Introduction

Pertussis, also known as whooping cough, is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. It is transmitted from person to person usually via coughing or sneezing or via close contact in an enclosed environment. Symptoms usually develop within 5 to 10 days after exposure, but sometimes not for as long as 3 weeks. Pertussis has an insidious onset with catarrhal symptoms that are indistinguishable from those of minor respiratory tract infections. The cough, which is initially intermittent, becomes paroxysmal. In typical cases paroxysms terminate with inspiratory whoop and post-tussive vomiting can follow. The cough typically persists for 1 to 6 weeks or more.

There has been an increase in the number of reported cases of pertussis since the 1980s worldwide. Several factors may have contributed to this observation, and these include:

- An increased awareness and recognition of pertussis among healthcare practitioners
- A greater access to and use of laboratory diagnostics, especially with polymerase chain reaction (PCR) technology
- An increased surveillance and reporting of pertussis infections to public health departments
- Waning immunity from vaccines

Rationale for antenatal tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccination

The main aim of antenatal Tdap vaccination is to provide passive protection to the neonate/infant via trans-placental transmission of antibodies (especially since Tdap vaccine can only be given to infants at 2 months of age). This is important as neonates/Infants are particularly at risk of serious disease as they remain vulnerable until they can be vaccinated at 2 months of age.

Unvaccinated or incompletely vaccinated infants less than 12 months of age have the highest risk of severe illness including hospitalization and death. In this particular group, about half need treatment in a hospital, most commonly in infants less than 6 months of age.

Of those infants with pertussis who need treatment in a hospital, approximately:

- 61% will have apnoea
- 23% suffer from pneumonia
- 1.1% will have seizures
- 1% will die
- 0.3% will have encephalopathy as a result of hypoxia from coughing or from toxins

Achieving passive protection in the neonate/infant via maternal pertussis antibodies would therefore help reduce the risks of pertussis infection in infancy and its potential complications as discussed above. Vaccination is recommended with each pregnancy to provide maximal protection to every infant as

vaccine-induced pertussis antibodies wane over time and the protective antibody level required in newborn infants is unknown.

There is no evidence of pertussis infection in pregnancy being more severe compared to the general population, nor is there any evidence that pertussis infection is associated with increased obstetric complications in pregnancy. There is also no evidence of pertussis infection in pregnancy being associated with an increased risk of fetal complications.

Information on the Tdap vaccine

- The Tdap vaccine is safe for use in pregnancy with studies showing no link between Tdap vaccine administration and increased risk of pregnancy complications such as low birth weight or preterm delivery.
- The vaccine is administered as a single dose intramuscularly, preferably at the deltoid area.
- Maternal immune response to the vaccine peaks about 2 weeks after administration.
- Common side effects experienced after Tdap vaccination include erythema, swelling, pain and tenderness at the injection site, body ache, fatigue and fever.
- Rarely, Tdap vaccines can cause serious problems such as severe allergic reactions. People who have had a severe allergic reaction (e.g. anaphylaxis) after a previous dose or a severe allergy to any of the vaccine components should not receive the vaccine.

CURRENT INTERNATIONAL GUIDELINE RECOMMENDATIONS

UK (Public Health England)	All women should be offered pertussis vaccination during each pregnancy, ideally between weeks 16 and 32 of pregnancy to maximize the likelihood that the baby will be protected from birth.
CDC Advisory Committee on Immunization Practices and American College of O&G (ACOG)	Pregnant women should receive a single dose of Tdap vaccine during every pregnancy, preferably at 27 through 36 weeks of gestation. Tdap is recommended only in the immediate postpartum period before discharge from the hospital or birthing centre for new mothers who have never received Tdap before or whose vaccination status is unknown.
Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	Tdap vaccine is recommended as a single dose during the 3rd trimester of each pregnancy. The optimal time for vaccination is early in the 3rd trimester between 28 and 32 weeks.

CURRENT LOCAL GUIDELINE RECOMMENDATIONS

Clinical Practice Guidelines on Adult Vaccination (April 2016)	Pertussis vaccination during the third trimester of every pregnancy is recommended regardless of interval from the last Tdap vaccination.
Ministry of Health (Singapore) National Adult Immunisation Schedule (NAIS)	Pregnant women should receive the Tdap vaccine between the 16th to 32th weeks of each pregnancy, so as to provide maximal protection to each infant, including pregnancies which are closely spaced (less than 2 years). Tdap can also be considered after 32nd week of gestation during each pregnancy. Maternal vaccination in this period may afford less protection for infants, but would potentially protect the mother from pertussis infection and thereby reduce the risk of exposure to her infant.

References:

- https://www.cdc.gov/flu/resource-center/freeresources/print/print-pregnant.htm#Vaccination
- https://www.cdc.gov/vaccines/vpd/pertussis/index.html

UPDATES ON

PRIMARY PREVENTION OF CERVICAL CANCER

A/Prof Timothy Lim Yong Kuei

Cervical cancer is considered a highly preventable cancer as it is mainly caused by persistent high risk human papillomavirus (HPV) infection, particularly by types 16 and 18 which account for up to 70% of all cervical cancers. The bivalent (2vHPV) and quadrivalent (4vHPV) vaccines have been in use for the past decade, and have been shown to be safe and highly efficacious. For maximal benefit, the vaccine should be given before the onset of sexual activity, as it does not protect against pre-existing HPV infections. Besides cervical cancer, we also know that HPV is associated with vulvar and vaginal cancer in women, penile cancer in males, anal and oropharyngeal cancer in both sexes.

The new 9-valent (9vHPV) vaccine was FDA approved in December 2014 and is the only approved HPV vaccine available in the United States today. The vaccine was launched in Singapore in April 2017 and has been approved for use in both young men and women aged 9 to 26 years. Several large trials were undertaken to demonstrate the efficacy, immunogenicity and safety prior to being FDA approved. The evidence is summarized as follows:

- In a phase III efficacy randomized trial comparing 9vHPV with 4vHPV vaccine in about 14,000 females aged 16 through 26 years:
  - the 9vHPV efficacy for prevention of ≥CIN2, VAIN grade 2 or 3, and VIN grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58 was 96.7% in the per protocol population.

- Few cases were caused by HPV 6, 11, 16, or 18 in either vaccine group.
- The 9vHPV vaccine generated anti-HPV 6, 11, 16, and 18 immune responses that were non-inferior to those generated by the 4v HPV vaccine.
- In the 9vHPV group, >99% seroconverted to all nine HPV vaccine types.
- The 9vHPV vaccine reduced the numbers of Pap test abnormalities and cervical procedures.
- The 9vHPV vaccine causes more injection site adverse effects compared to the 4vHPV vaccine but the systemic adverse effects are similar. The most common injection-site adverse effects were pain, swelling, erythema, and pruritus whereas the most common vaccine-related systemic adverse effect in both vaccines was headache.
- As with the 2vHPV and 4vHPV vaccines, vaccination with the 9vHPV vaccine should be postponed till completion of pregnancy. Nevertheless, current data does not indicate any increased risk of malformation or fetal/neonatal toxicity in pregnant women.

- In the immunobridging study involving 1800 girls and boys aged 9 to 15 years compared to women 16 to 26 years, the immune responses for the adolescents were found to be non-inferior to those in women. In both females and males, >99% seroconverted to all 9 types, and the geometric mean titres(GMT) in boys were noninferior to those in girls.

- In another immunobridging study involving 1400 males age 16 to 26 years compared to women 16 to 26 years, the GMTs for all 9 HPV types were noninferior in heterosexual males compared to the women but the GMTs were slightly lower in men having sex with men (MSM) compared with heterosexual males and women.

- With regards to giving the 9vHPV vaccine to women with prior 4vHPV vaccine (>12 months interval), a study was performed and 924 women were randomised to placebo or the 9vHPV vaccine. The GMTs against HPV Types 6, 11, 16, and 18 showed evidence of an immune memory response in prior 4vHPV vaccine recipients and immunogenicity was demonstrated with respect to HPV Types 31, 33, 45, 52, and 58 in prior 4v HPV vaccine recipients. Hence, the 9vHPV vaccine can be given to those with prior vaccination.

- In a recently concluded study comparing the immunogenicity of the 2 dose and 3 dose regimens of the 9v HPV vaccine, the 2 dose schedule was shown not to be inferior to the 3 dose in both girls and boys age 9 to 14 years. Furthermore, the HPV antibodies were found to be higher in those who receive at a 12-month interval than in those at 6-month interval. The 2-dose schedule has cost saving and pragmatic advantages that may facilitate a higher coverage.

APPROVED RECOMMENDATIONS IN SINGAPORE 2017

INDICATIONS	GIRLS AND WOMEN 9-26 YEARS OF AGE	BOYS AND MEN 9-26 YEARS OF AGE
Cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58		
Cervical	✓*	
Vulvar	✓*	
Vaginal	✓*	
Anal	✓*	✓
Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58		
Premaglinant cervical lesions	✓	
Premaglinant vulvar lesions	✓	
Premaglinant vaginal legions	✓	
Premaglinant anal legions	✓	✓
Cervical adenocarcinoma in situ	✓	
Genital warts caused by HPV types 6 and 11	✓	✓
HPV infections caused by HPT types 6, 11, 16, 18, 31, 33, 45, 52, and 58	✓	✓
Dosage: 3 Dose (0, 2 and 6 months)	✓	

For 9 to 14 years, the 2 dose regimen can also be used at 0, 5-13 month interval.

References:

- A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. Joura EA et al. N Engl J Med. 2015 Feb 19;372(8):711-23. doi: 10.1056/NEJMoa1405044.
- Immunogenicity and safety of the 9-valent HPV vaccine in men. Castellsagué X et al.Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2

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MCI (P) 126/08/2017