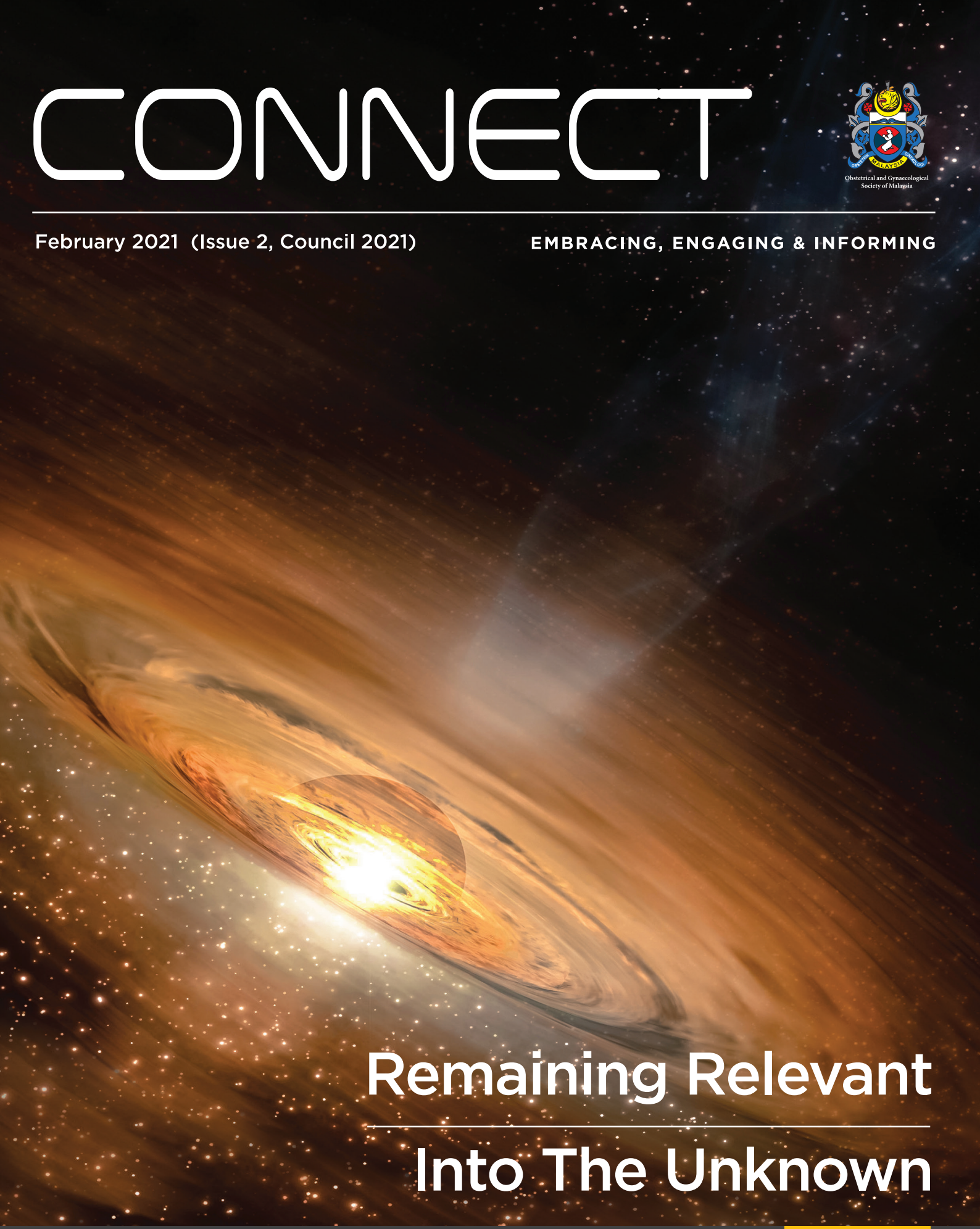
CONNECT

Obstetrical and Gynaecological Society of Malaysia

February 2021 (Issue 2, Council 2021)

EMBRACING, ENGAGING & INFORMING



Remaining Relevant

Into The Unknown

Onco-fertility

28th OGSM Congress is Back

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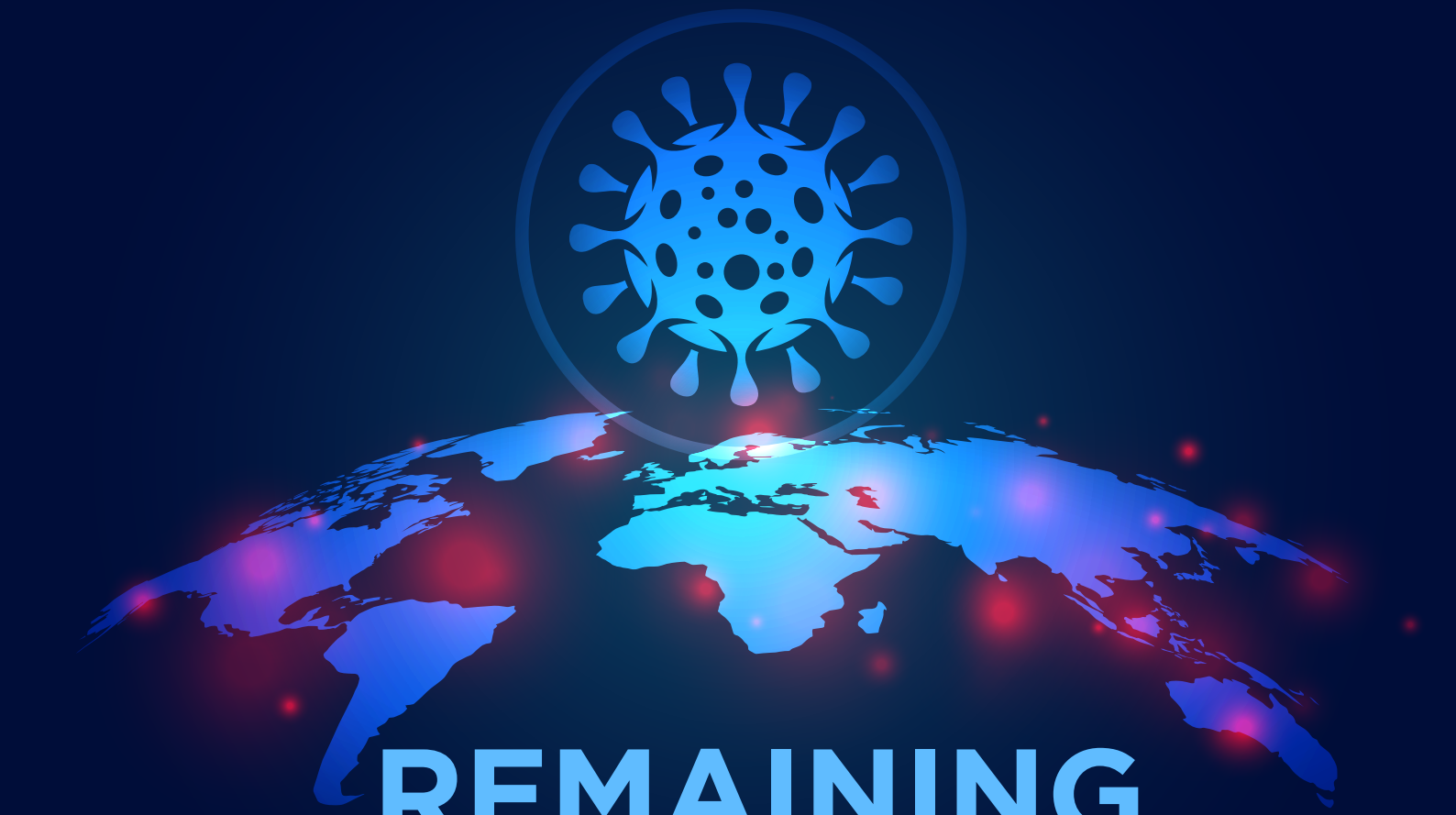
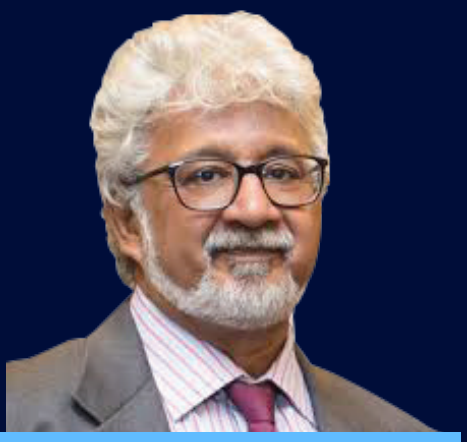


REMAINING RELEVANT



Dr Muralitharan Ganesalingam
President, OGSM

In December 2019, an epidemic of pneumonia of unknown cause emerged in Wuhan, China. In early January 2020, a virus was sequenced and identified as a novel coronavirus named SARS-CoV-2, the causative agent of COVID-19. By March 2020, the World Health Organization (WHO) declared the outbreak a pandemic. Today, worldwide, the global cumulative total of Covid-19 cases has crossed the 80 million mark with more than 1.7 million Covid-19 fatalities.

The United States Institute for Heath Metrics and Evaluation (IHME) projections serve as a warning to expect the worst that can happen and emphasizes the need for countries to embark on urgent remedial measures to control the spread of the virus. Going by IHME projections, Malaysia would experience a continuous rise in the number of Covid-19 infections until mid-March 2021, with numbers rising to more than 5,000 daily infections from late February 2021.

Professional Organisations must be prepared to change the way they structure, think and behave, in order to meet the rapidly evolving needs of their members during COVID-19 crisis. The Council needs to gauge how the members feel during these times of uncertainty. We need to redesign how we remain relevant to our members. We need a strategic view to identify what our members need and what OGSM needs to do to continue to resonate with its members.

It is unlikely that we will be bouncing back to normal anytime soon. The OGSM Congress scheduled for July 2020 was postponed and has currently been planned for July 2021. Will we be out of the woods by

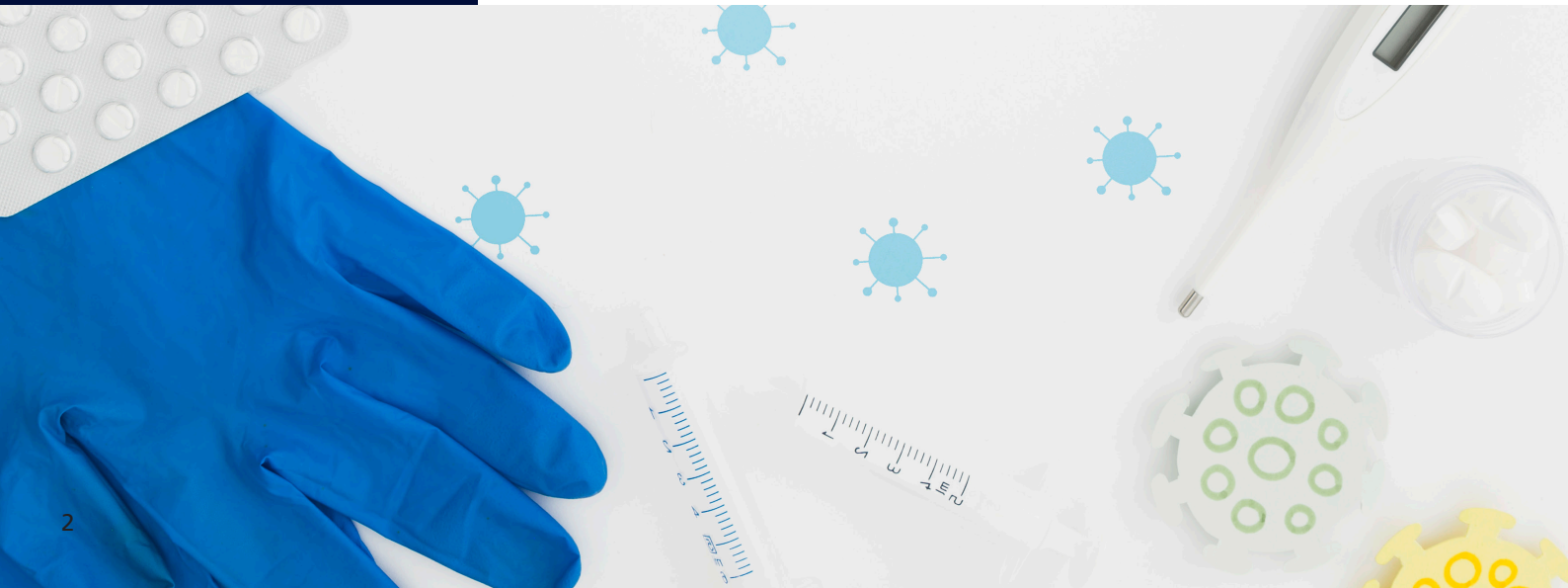
then? Will the Congress continue to be a large physical gathering, or do we need to improvise and plan a fully virtual or a hybrid congress?

Medical talks by the industry was the way in which knowledge and innovations were imparted to the members. Now, with the health crisis such talks would be considered a health hazard and we need to come up with novel methods of keeping our members informed of innovations in our discipline, maintain the professional development of the members as well as ensure that members have access to Continuous Professional Development (CPD) points.

While the OGSM is one of the largest professional medical societies, it is also an expensive organization to maintain. The yearly congress has been our source of income and fortunately this yearly source of revenue has been enough for maintaining the Society for the entire year. Now with the Covid-19 crisis in 2020, access to this resource was abruptly terminated, triggering the Council to experiment with alternative methods of generating income. We have been fortunate in that the previous Councils have been prudent in their spending and OGSM as a society has adequate reserves to tide us through these trying times.

The Council recognizes that the financial viability of some practices, especially those not connected to larger systems may be hampered. The Council needs to think of ways in which knowledge could be imparted to allow members to re-create their approach to patients by acquiring new skills in office Obstetrics and Gynaecology. These virtual professional development events will need to be packaged and presented so as to allow members to plan their calendar in advance.

“Anyone can hold the helm when the sea is calm”. As with all crises, when this one finally subsides it will provide ample learnings for us on how to navigate through times of uncertainty.



Dr Voon Hian Yan
Maternal Fetal Medicine Specialist
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INTO THE "UNKNOWN"

Dr Tan Cheng is an Obstetrician & Gynaecologist currently based in Tung Shin Hospital, Kuala Lumpur. He is passionate in the training of MRCOG candidates and has been active in applying the advances of information technology in day to day medical practices as well as teachings

Dr Lee Chui Ling is a Consultant Obstetrician and Gynaecologist who is practising in Kempas Medical Centre, Johor Bahru.

Dr. Chuah Joo Ngor is an Obstetrician & Gynaecologist based at Pantai Hospital Ipoh, with special interest in Minimally Invasive Surgery.

-3 different states. 3 different personalities. All took a leapt of faith into private practice-

While serving the goverment is highly rewarding for some, others may have "pull" or "push" factors to consider, not unlike deciding which maneuvre to perform during a deeply-engaged second stage caesarean. CONNECT catches up with young obstetricians & gynaecologists who have recently chosen to venture out to the Ice Castle on the North Mountain (N.B this was written shortly after the Movement Control Order began in March 2020 and an overdose of a Disney franchise)

Where and how long have you been in private practice?

TC: It has been 1 year since I have joined a private hospital in the Klang Valley.

CJN: I have been in my current hospital in Ipoh for exactly a year.

LCL: I started 9 months ago in a family-owned medical centre.

Is life in private practice what you expected?

TC: To a certain extent. I can now provide detailed follow-up care for my patients from the moment they step into my clinic. It is an extremely important factor when I decided to become a doctor-besides building good rapport, I can monitor their progress thoroughly and provide personalised care for them. This is limited in government hospitals due to the vast amount of patient load, the changes in the rotation and coverage areas. On top of that, I have more time for my family and myself after work.

CJN: Oh yes. Flexibility is there. I can always arrange my schedule according to my own timing. Defnitely more time for personal stuff (maybe because I'm not too busy yet). However, the time I do have, is more unpredictable in private practice. As you may be aware, labouring mothers can turn up anytime!

LCL: Not quite. In the initial months, I saw few patients per day. Sometimes I find myself sitting on the desk, watching minutes tick by. I'm embarrassed by this, but I also have the strangest feeling of detachment from it all. I made good use of my time by doing some research papers, conducting online class for Women Health Module in Monash University and also conducting Facebook live sessions to increase visibility to the public. On the other hand, I was grateful for the extra time with my daughter and being around more for my family.

What is the most challenging aspect of your job?

TC: In government hospitals, when you are not oncall, you do not have to worry about being asked to go back to the hospital. However in private practice, I find that keeping track of every patient's progress is crucial before planning my day-to-day activities.

CJN: I am all alone. The fear of complications haunt me from time to time and despite the experience, self-doubt creeps in. When a patient complains of pain post-operatively, thousands of questions start playing in my mind. Was the uterus perforated while dilating the os? Was the bladder or ureter injured when doing the hysterectomy?

LCL: Understanding patient psyche. I once suggested treatment in a public facility for a self-paying patient with purported financial constraints. However, she was adamant to continue her care with us and pressed for a discount. After discussion with the management to obtain approval for a discounted price, I found out she checked herself into our exclusive private suite.

What is the most satisfying aspect of your job?

TC: I find collaboration among different practices for a common goal the most satisfying. My hospital is unique as it is founded as a not-for-profit organisation, aiming to provide holistic and affordable healthcare services through Western and Traditional Chinese Medicine. Both Western Medicine Consultants and Traditional Chinese Medicine Practitioners are constantly exchanging experiences and

CJN: Patients' appreciation. The "Thank you so much Dr" or "I can't thank you more" is the most heart-warming part of my job. Contrary to public perception, it is not always about the money. At times, you would offer your services pro bono as, not all patients who go to a private facility are well-off or have insurance coverage. Some patients are desperate and have financial constraints. However, at end of the day, this appreciation,

LCL: Able to listen to patients and support them to make informed choices about their health more than I could previously.

knowledge to enhance the services provided to patients. For example, we go through the properties of postpartum care herbal packs together, and make adjustments so that it would not cause any potential bleeding among post-caesarean section mothers.

Being a not-for-profit organisation, our primary aim is to ensure that the medical services are sustainable, therefore the services provided are at a much lower rate in comparison to other private hospitals. Ever since the government imposed the rulings of full healthcare charges for non-residents, we have seen a surge of foreign nationals, as the charges imposed are comparable.

however small, is re-invigorating and gives you the strength to continue doing what you do.

How has Covid-19 affected your practice?

TC: I have seen a surge in obstetric patients during COVID-19 as most private practices require mothers to be screened when the pregnancy is at term. Even though this increased the costs, most mothers found it reassuring knowing that the ward was safer, as screening has been done. As for the gynaecological cases, there is a decline for follow-up as most of these appointments can be deferred to a later date.

CJN: Covid has shut down the entire global economy. My practice was not exempted. During the inital phase of MCO, many patients were not willing to come to hospitals in fear of contracting the virus. All elective cases had to be deferred and operating in full PPE was a challenge. All these are new to most of us, I guess.

From this pandemic, I learn that many things are more valuable than dollar and cents. Looking at the number of positive cases and the death rates increasing everyday makes me treasure what I have right in front of my eyes and be contented. Spend time with your loved ones. You will never know what is waiting for you next. Stay safe, stay healthy and may God bless you.

LCL: My practice was not affected much since the patient load was not high initially.

P.S Contents received have been edited for clarity. Honest opinions were provided by the young doctors, which, not unlike MCO SOPs, may have changed by the time of publication.

Compiled by Dr Voon Hian Yan
Maternal Fetal Medicine Specialist
Sarawak General Hospital

AGM 2020

Dr Loh Huey Wen
Hon. Secretary, OGSM

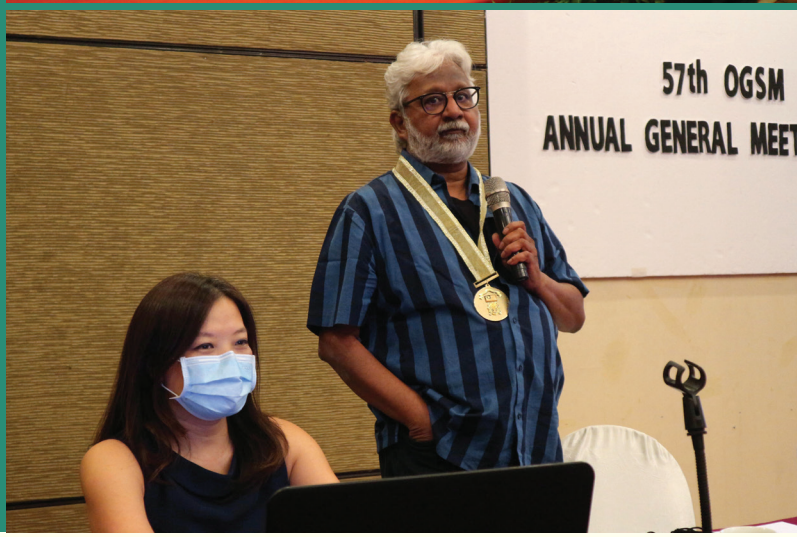
Hon. Secretary's Report

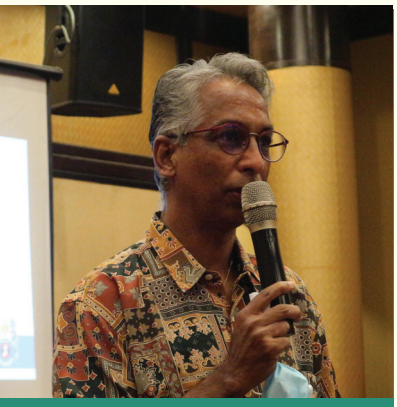
2020 was a difficult year. The COVID-19 pandemic changed the way many organisations ran things and OGSM was no exception. The annual general meeting is traditionally held in June in conjunction with the annual OGSM Congress. In compliance with directives from the Malaysian government and the implementation of the Movement Control Order (MCO), the 28th OGSM congress was delayed and then postponed.

After lengthy discussions with the Registrar of Societies (ROS) and legal consultations with OGSM's lawyers, the AGM was called for the 10th October 2020 at the Bukit Kiara club, coincidentally, on the 57th anniversary on the formation of OGSM. Despite the challenges, the attendance was good. Dr Haris Suharjono could only attend virtually as Sarawak had imposed travel restrictions a few days prior to the AGM. The meeting was chaired by the President Elect, Dr Murali, in compliance with our constitution.

There was active participation from those who attended the AGM with healthy discussion aplenty. Quite a few issues were put to rest at this AGM whilst a few more arose. The elections were lively and saw the participation of many new, young faces. I would like to record OGSM's appreciation and gratitude to Dr Haris for his leadership in the past year as he dealt with numerous challenges caused by COVID-19.

The newly elected council under Dr Murali has since knuckled down. The Covid-19 pandemic is unlikely to go away soon. The council and secretariat are trying to adapt as best we can to weather this pandemic to ensure OGSM emerges unscathed. We hope to have your continual support as we navigate these uncharted waters.


57th OGSM
ANNUAL GENERAL MEE

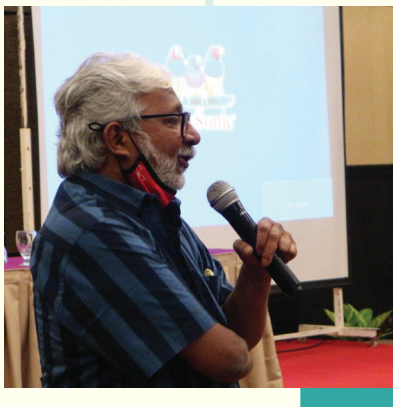


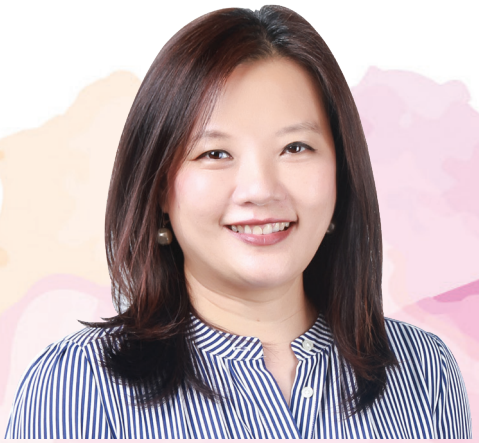










Dr Hoo Mei Lin
Organising Chairperson
President-Elect 2020/2021

We are back!

23rd-25th July 2021.

We are pleased to announce that the 28th OGSM Congress has been confirmed for the 23-25th July 2021. We initially aimed to hold a physical congress but fortunately realized early that it was unlikely to be pandemic free by July 2021. Therefore with this in mind, we were initially planning for this congress to be a hybrid one with a virtual component to compliment the traditional congress. Now that the pandemic has only gotten worse rather than better, we have made a firm decision to proceed with a purely virtual congress. Come what may, the congress will go on.

The committee has been working hard to find a suitable partner to run the virtual congress. This year will be far more challenging financially as traditionally, the annual running of the OGSM office has been fully funded by the proceeds of its annual congress. This did not happen in 2020, even with a very successful virtual conference. With this in mind, we will have to be frugal to maximize our returns to ensure that OGSM remains financially viable.

We hope to have your support in these trying times. Stay tuned for more updates either here or on our social media platforms.

Happy Lunar New Year. Stay Safe.

Cell Free DNA Screening: Lest We Forget

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Fetal anomaly screening has 2 important components: aneuploidy and structural. This article focuses on the former. The combined first trimester screening (FTS) has been the benchmark for aneuploidy screening (especially for trisomy 21) for 3 decades and counting. The 20 weeks fetal anomaly scan remains the gold standard for structural screening.

Maternal serum cell free fetal DNA (cfDNA) was first discovered in 1997 by Dennis Lo and team. Based on the fact that placental cell apoptosis happens regularly fetal DNA sequencing resulted in the rapid introduction of cfDNA into aneuploidy screening. The first 'non-invasive' prenatal tests (NIPT) appeared at the turn of the millennia. The rest as they say is history.

cfDNA is currently run via one of the sequencing protocols or single nucleotide polymorphism technique (SNP). In short, fetal-placental DNA is distinguished from maternal and the quantum of DNA then compared to that of the euploid mother's. A threshold of fetal DNA load is required for valid calculations. This is the basis of reporting on fetal fraction (FF), a mandatory mention for the validity of reporting.

Any discussion on screening tests invokes our deepest fears in facing the face contorting and mind numbing litany of statistical juggernauts. A glossary has been included to ease this phase and promote a smooth read.

The debate of diagnostic vs screening

With detection rate approaching 100% the number of private industries offering the tests has mushroomed. Natera, verify, harmony, BGI were among the leaders. Locally DNA Laboratories and Genomix offer the test. As good a test it may seem cfDNA tests all fall under the category of "screening" tests. There are false negatives – our biggest fear, and there are false positives – more common than we think. It would be a misconception to suggest that cfDNA tests are diagnostic..

Causes of false positive tests include: vanishing twin, maternal malignancy, maternal and placental mosaicism, maternal copy number variation (CNV), recent blood transfusion from male donor and chance (1-2/1000). Causes of false negative outcomes include: placental mosaicism (via a varying pathway), borderline low FF and maternal CNV via differing pathway. Clinicians should broaden management beyond the status of the fetus.

Positive predictive value (PPV) is key

The prevalence of the condition tested for is a prerequisite for accurate measurement of sensitivity and specificity, in turn, forming the key prerequisites to counselling positive and negative predictive values. Large prevalence studies are lacking in Malaysia. ALL NIPT risk calculations here are based on a set standard foreign cohort.

The negative predictive value (NPV) of most cfDNA providers have hit the 99.99% mark with next generation sequencing (NGS). cfDNA has an excellant pick-up rate. The PPV of tests however, the mark of a truly good test, varies among providers and population tested. It is consensus that only labs that list their PPV for conditions screened should be utilized. Likewise, clinicians should only select conditions that would have a PPV returned by providers to be screened.

Table 1: PPV of conditions screened by cfDNA in a 37 year old. (Panorama)

Condition	Sensitivity (95% CI)	Specificity (95% CI)	Positif Predictive Value	Negativee Predictive Value
Trisomy 21[1,2,3,4]	>99% (CI 97.8-99.9)	>99% (CI 99.7-100)	91%	>99.99%*
Trisomy 18[1,2,3,4]	>98.2% (CI 90.4-99.9)	>99% (CI 99.7-100)	93%	>99.99%*
Trisomy 13[1,2,3,4]	>99% (CI 87.2-100)	>99% (CI 99.8-100)	38%	>99.99%*
Monosomy X[1,2,3,4]	94.7% (CI 74.0-99.9)	>99% (CI 99.7-100)	50%	>99.99%*
Triplody X[5,6]	>99% (CI 66.4-100)	>99% (CI 99.5-100)	5.3%	>99.99%*
XXX, XXY, XYY[4]	N/A-Reported when identified	N/A-Reported when identified	89%	N/A-Reported when identified
22q11.2 deletion syndrome[7,8,9]	90.0% (CI 55.5-99.7)	>99% (CI 98.6-99.90)	20%**	99.97-99.99%***
1p36 deletion syndrome[7,8]	>99% (CI 2.5-100)	>99% (CI 99.1-100)	7-17%***	99.98-99.99%***
Angelman syndrome[7,8]	95.5% (CI 77.2-99.9)	>99% (CI 99.1-100)	10%**	>99.99%*
Cri-du-chat syndrome[7,8]	>99% (CI 85.8-100)	>99% (CI 99.1-100)	2-5%***	>99.99%*
Prader-Willi syndrome[7,8]	93.8% (CI 69.8-99.8)	>99% (CI 99.1-100)	5%**	>99.99%

Note: PPV drops as the prevalence of conditions drop.

PPV falls with the prevalence of the condition tested in the given population. As an example, the chance of the baby actually having trisomy 21 after a positive cfDNA in a 37 year old is 91% with a 9% FPR. A 27 year old client with positive screen would only have PPV of only 54%. A recent UK lawsuit puts this precise scenario into light. The risk of a procedure related miscarriage from a false positive is real. In a whole population study cfDNA screening returned a 4-5% positive yield with only 1 in every 15-20 subsequent diagnostic testing confirming aneuploidy. As we approach universal screening, our pre-test counselling has to be in congruent with the risk stratification of screened subjects.

PPV is essential in the counselling of any screening test. We utilize the PPV calculator at https://www.perinatalquality.org (ACOG endorsed in 2015)

What conditions should be screened by cfDNA?

It all started with screening for Down syndrome, the most common aneuploidy that eluded scrutiny by the ultrasound scan. The advent of first trimester screening saw Edward and Patau syndromes included into screening as the 3 formed 70% of all aneuploidies encountered. From a practical point of view, the core business of FTS remains Down syndrome as the other 2 are mostly detected by ultrasound albeit at later stages. At the dawn of the cfDNA the 3 most common aneuploidies were scrutinized.

The next phase saw the inclusion of certain "common" microdeletions into the fray. Starting with the 22q11.2 (DiGeorge) deletion which had a prevalence close to that of T21, now we see Prader Willie, cri-du-chat, 1p36 and Angleman included into the package. This is an industry led phenomena and not a public health one. With the increasing scramble for a share of this lucrative market providers have included many other supplementary conditions screened. The lower the prevalence the lower the PPV (Table 1). The justification for inclusion of these microdeletions were that their prevalence were high enough or comparable to established conditions screened for like Down syndrome.

We now see whole genome scrutiny of all chromosomes by some cfDNA providers. This not only is unvalidated but the supplementary aneuploidies are so rare that the PPV is likely to be insufficient for the test to qualify as screening test. Most aneuploidies involving chromosomes other than 13, 18 and 21 almost always result in early miscarriage or severe systemic anomalies detectable by ultrasound. Most screen positives are false positives due to placental mosaicism. True mosaicism for the supplementary chromosomes are rare begging the question why offer it in the first place and then go to pains to justify it when faced with the prospect of invasive testing with a low PPV. Referrals for positive cfDNA for supplementary chromosomes are on the rise and they carry a significant risk of invasive testing and its attendant risk of pregnancy loss.

Guiding organizations such as the ACOG and the European ESHG/ASHG recommend cfDNA for the screening of chromosomes 13,18,21 and the sex chromosomes. The RCOG NIPT guidance is eagerly anticipated due this year.

Who should be screened?

Down syndrome OR common aneuploidy screening and testing options SHOULD be discussed with all clients as the group of anomalies fall under the broader fetal anomaly screening context. Clients can then be given the following options:

1. To decline knowledge of possibility of aneuploidy.
2. Screening options:
   a. NT and NB (with or without other ultrasound parameters) – 70% sensitivity.
   b. Combined FTS – 85%-95% sensitivity (depending on number of ultrasound parameters included) with 5% FPR (FPR).
   c. The quadruple test – 90% sensitivity, 5% FPR.
   d. cfDNA –99% sensitivity and specificity with varying NPV depending on the prevalence in the given age group.
3. Invasive diagnostic testing for common aneuploidy: with associated procedure related pregnancy loss rate.

So which lab should I use?

This is multifactorial. Cost has played a major role. As costs stabilize some factors may be used as a guiding principle. If scientific principles are to go by the decision on which laboratory should be made by the following criteria:

a. Utilizing next generation sequencing (NGS) – Most labs now utilize one form of NGS or the other. Providers using the SNP method have added advantage of marginally superior NPV and PPV as maternal DNA is accurately distinguished.
b. Utilizing local aneuploidy and microdeletion prevalence data – None exist. Age related standard references have been adopted. Only with local data can accurate positive predictive value be provided.
c. Well published data on sensitivity and specificity and false positive and negative rates. Laboratories that publish their outcome data are also publicizing their openness to scrutiny and this is turn is a measure of integrity. Most of the cfDNA counselling data on outcomes and shortcoming have come from published foreign data.
d. Laboratories that do not over breach the boundaries of general consensus.
e. Providers that offer quality and easily accessible genetic counselling when faced with a clinical situation.
f. Labs with higher FF cut off's.
g. Labs that list PPV and NPV for all conditions tested and reported.

How then, do we proceed?

1. The basics of fetal anomaly screening should be practised:
   a. First trimester scan (FT Scan) for aneuploidy markers: 11 to 14 weeks.
      Anomalies and positive aneuploidy markers are exclusion criteria for cfDNA.
   b. 2nd trimester scan for structural anomalies.

This has been shown to reduce perinatal mortality and morbidity rates.

2. Options for those requesting early and superior aneuploidy screening.
   a. Ultrasound based risk calculation at week 11-14 (licenced propriety software required) OR
   b. Combined FTS, both between 11-14 weeks. OR
   c. cfDNA

   Tier based recommendations may be a practical way forward: Readers are directed to discussion on reflex and contingency based screening models.

   It is indeed because of the limitations and uncertainties described that cfDNA is mainly utilized as secondary screening after the combined FTS. ACOG, NHS and the EU recommend cfDNA as secondary screening highlighting that universal screening may increase the number of unnecessary invasive procedures in the low risk group, causing more harm than good.

   It would thus seem prudent to offer cfDNA screening AFTER a normal FT-Scan.

3. cfDNA counselling should involve all conditions listed by the providers and not just T21. This is tedious and time consuming yet must be managed in a practical manner by clinicians advocating the tests.

What are the potential scenarios after cfDNA testing?

1. Negative test
2. False negative test: the miss rate is 1 in 10,000. Very rare but still a possibility.
3. Positive test:
   a. Standard chromosomes: invasive testing recommended.
   b. Supplementary chromosomes: invasive testing recommended, option of conservative management if the fetus is normal on detailed fetal anomaly scan.

PEARLS of NIPT

- It is not a diagnostic test and can miss detections.
- It is a screening test and diagnostic testing is also an option.
- cfDNA is still widely only recommended for the scrutiny of chromosomes 13,18,21 X and Y.
- When disclosing result avoid the term "NORMAL" – screening is either Positive (High Risk) or Negative (Low Risk).
- Diagnostic testing is indicated when the test is positive (High Risk)
- Discussing age related PPV in pre-test. Screening may lead to a procedure related miscarriage after a false positive.
- The under prepared patient: lack of adequate pre-test counselling.
- cfDNA contraindicated in the following: vanishing twin, higher order muliples, abnormal FT-scan (the nuchal translucency is > 95th centile OR ≥ 3mm)

Pitfalls

- Not requesting a First Trimester Scan because cfDNA opted.
- Recommending decision based on the cfDNA result.
- The FF is lower in the following conditions causing lower detection rate: obesity, twin pregnancies, donor egg conception, surrogate mothers, anticoagulation (LMWH < 20 weeks)
- Tests utilizing the SNP method are not suitable for the following: donor egg, surrogacy and marrow/ organ transplant recipient. Sequencing methods should be utilized instead.
- Gender reveal can be a crime in various countries.
- Testing on unprepared patients: suboptimal pre-test counselling.
- 2-3% of all cfDNA should be reported as NA. Monitor providers who breach thresholds for commercial or competitive benefits.

4. False positive: see 2nd paragraph
5. No analysis (NA): low total FF, low fragments/ sequenced or increased homogeneity (uniparental disomy or consanguinity). Low FF is the most common cause and occurs especially in early testing (providers have brought the validity of test gestation to 9 or 10 weeks) or obesity and twin pregnancies (see PITFALL BOX). It is also known that aneuploidic fetuses have lower FF. Some providers may distinguish this and advise invasive testing. Others apply a blanket re-sample strategy. If the repeat is also NA invasive testing is justified.
6. No analysis: vanishing twin. Most providers would distance themselves from this scenario as it would be difficult to distinguish the source of a discordant result. Hence it is a contraindication of sorts for cfDNA.

GLOSSARY

Statistical terms	What it means?
Sensitivity	Sometimes called the "Detection Rate". This is the proportion of those who has the condition in a screened population who is screened positive.
Specificity	The proportion of people who are screened negative who do not have the disease.
False Positive Rate (FPR)	This is the proportion of all negatives that still yield positive test results. The FPR is a measure of accuracy for a test.
False Negative Rate (FNR)	This is the proportion of all positives that yield negative test results. It improperly indicates no disease when, in reality it is present.
Positive Predictive Value (PPV)	It is the probability that a person with a positive screening test truly has the disease.
Negative Predictive Value (NPV)	It is the probability that a person with a negative screening test truly does not have the disease.
Likelihood ratio	The ratio of the odds of the disease in someone who screens positive or negative to the odds of the disease in the general population.

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Onco-fertility

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Advances that will make a difference in years to come .. yet the long journey needs a beginning.

The word "Onco-Fertility" was first coined by Dr Teresa K Woodruff in 2007 in a symposium held in University of Calgary called 'Pushing the Boundaries' – Advances that will change the world in 20 years. She introduced the word Onco-

Fertility for the first time in her lecture that day and that's how the story began. A word that describes the intersection of two disciplines oncology and fertility, a word that carried the hope that one day this field will change the world for young cancer women who have been left out of the equation for far too long.

The field of onco-fertility began with an urgent unmet need for young cancer patients. It encompasses the discussion of risk to fertility and fertility preservation (FP) options, as well as the management of related complications such as pubertal delay, menstrual irregularities, hormonal deficiency and sexual dysfunction[1]. Infertility occurs when cancer treatments damages gonadal tissue, gametes or sex hormones. In males, cancer treatment may affect spermatogenesis or the production of LH/FSH in the pituitary or testosterone production from Leydig cells in the testes and affect pubertal development and sexual function. The human ovary has a fixed number of primordial follicles and the follicles contain oocytes which are lost progressively with increasing age, resulting in menopause which at an average occurs around 50 years of age. Cancer treatment accelerates the follicle and oocyte depletion leading to premature menopause.

Cancer in adolescents and young adults (AYAs) is defined by the National Cancer Institute as diagnosis occurring among those aged 15-39 years and is unique from cancer diagnosed in other age groups because of important differences in the distribution of cancer types, tumour biology and prognosis[2]. In addition, compared with older patients with cancer, AYAs have a higher risk of long-term and late effects including decreased reproductive and sexual function, psychological effects and premature menopause related health problems in female survivors[3]. From the cancer registry in the United States for 2020, there will be approximately 89,500 new cancer cases and 9270 deaths in AYAs[4]. In Malaysia, according to the Malaysian National Cancer Registry Reports between 2007-2011 there were 103,507 new cancer cases reported and out of this 12,000 cases reported belonged to those aged between 18-40 years old. AYA patients are more likely to get certain types of cancers compared to older people, such as Hodgkin lymphoma, leukaemia, testicular cancer, thyroid cancer, breast cancer and some forms of sarcoma[4]. Among the female cancer survivors who were under the age of 40 years at diagnosis, the chance of achieving pregnancy was 20% lower in those diagnosed as children and 50% lower in those diagnosed as young adults compared to female siblings without cancer[5].With the current improvements in cancer survival rates and the awareness of the effects of cancer treatments on long-term health and fertility in this group of young people we should provide and educate them about FP options that are now available.

A cancer diagnosis in a young person seems particularly shocking and is understandably accompanied by an urgency to begin treatment. As such many practitioners may assume that young adults are solely interested in survival and not some far-off future risk to fertility or endocrine health. Yet assessment of the attitudes of adult survivors of childhood and young adolescence told us a very different story. Young women and their parents alike wished that they had fertility preservation options made available to them before they started treatment[5,6]. As for many of these adult survivors, their cancer treatment had become a distant memory , but the issue of infertility remained as a real and present problem that limited their social life and curtailed their hopes of a biologic family[7]. Concerns about fertility represents a major issue for young women and men with cancer, regardless of their age and the extent of the disease. Studies suggest among young female patients, cancer related fertility is associated with a greater risk of emotional distress and poorer quality of life[7]. The 2018 American Society of Clinical Oncology (ASCO) recommendation is for health care providers (medical oncologists, haematologists,

gynae-oncologists) to address the possibility of infertility as early as possible before treatment starts[8]. All international guidelines support referral to a specialist who can provide expert discussion and assessment about risk of reproductive harm and potential options for FP in women and men of reproductive age group before commencement of cancer treatment[9]. There is always the concern on who should be referred to a fertility specialist prior to cancer treatment. Onco-fertility counselling should be individualized and discussion of both the absolute benefits of the proposed anticancer treatment and the risk of infertility for each individual based on patient related factors such as age, comorbidities ,ovarian reserve in women and the sterilizing potential of the treatment proposed[9]. In some situations the risk of treatment-related infertility can be difficult to estimate due to limited data.

Making decisions about preserving future endocrine function and fertility requires that young cancer patients weigh information from many different sources, their doctors, families, society and all this happens at a highly emotional and difficult time when they are facing the most difficult situation in their life and their future for survival. As with any decision, patients need to fully understand and be aware of and understand the options and this can be particularly challenging for patients who have just received a cancer diagnosis and must make decision within a tight time frame. Fertility interventions in the conventional infertility settings are not urgent and patients are fully aware of their fertility status and these group of patients are some of the most well-knowledgeable patients about the treatment options that are available to them. In contrast, the young cancer patient is not generally aware of their reproductive health or fertility concerns, so the discussion about fertility options requires a team of reproductive medicine specialist, oncologist, surgeons and nurses to describe to them the potential impact of their treatment on endocrine and reproductive outcomes for them to understand before making the difficult decision in an already difficult situation. There are also the issues of logistics to care and financial constraints that can influence the decision-making process. In our setting, oncology cases for potential fertility preservation are referred to the reproductive medicine team and cases are seen within the next 24-48 hours to explain the options available. In difficult cases, a multidisciplinary team meeting with the oncologist, reproductive medicine team, surgical team,pathologist and patient is beneficial in decision making and certainly helps the patient make an informed decision.

Back in 2005, when oncofertility programs were just starting, men and pubertal boys were regularly offered sperm banking as an option to preserve their fertility prior to cancer treatment. Yet young women who had the same hope for survival had few to no fertility preservations made available to them. However today since the advancement in freezing techniques for oocytes, embryos and even ovarian tissue and with the advancement in Invitro fertilization (IVF) the situation has changed.

Ministry of Health started with adult male oncofertility preservation in 2009 with sperm cryopreservation for young adult males with cancer. This is the simplest to do as seminal fluid can be obtained from masturbation and centrifuged to obtain good quality sperms that are cryopreserved. However, we are not yet able to provide statistics for the life birth outcome as most cancer patients are young males and the outcome will be seen much later in years to come. For azoospermic men, more invasive surgical techniques were started few years later with sperm extraction such as testicular sperm extraction (TESE), testicular sperm aspiration (TESA) or percutaneous epididymal sperm aspiration (PESA) to obtain sperms and cryopreserved for use later.

Female oncology preservation program involves oocytes, embryo tissue cryopreservation which are both now established FP methods available in our setting and we hope to start ovarian tissue cryopreservation in the near future which is done on a research basis in Malaysia. Today, we have a well-established subsidized IVF-embryo cryopreservation for our young cancer women that is certainly helpful for these group of women.

More flexible ovarian stimulation protocols for oocyte collection are now available. Timing of these procedures no longer depends on the menstrual cycle in most cases and stimulation can be initiated with less delay compared with the old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day-independent schedule. Previously there was concern regards to estrogen-sensitive breast and gynecologic malignancies, the possibility that fertility preservation interventions may increase risk of cancer recurrence. However today with aromatase- inhibitor based stimulation protocols which are well established and the short duration of ovarian stimulation during oocyte retrieval does not increase the risk of cancer recurrence in these group of women[11-12]. The only challenge that we have is timing - as the standard procedure for embryo and oocyte cryopreservation requires controlled ovarian hyperstimulation and oocyte retrieval, a process that requires approximately 12-16 days. If chemotherapy cannot be postponed for this period of time without potential compromise to the patient's immediate or long-term treatment outcomes, then other fertility preservation options should be explored.

Breast cancer is the most common cancer affecting women in Malaysia and 20% of women are below the age of 40 years old[13]. Temporary ovarian suppression using luteinizing hormone-releasing hormone agonists (LHRHa) during chemotherapy to preserve ovarian function and fertility of breast cancer patients is associated with a reduced risk of chemotherapy-induced premature ovarian insufficiency and seems to increase the pregnancy rates, without an apparent negative consequence on prognosis of the disease[14-16]. In a meta-analysis of randomized studies, a total of 12 RCT's including 1231 breast cancer patients demonstrated that the use of LHRHa during the course of chemotherapy was associated with a significant reduced risk of premature ovarian insufficiency (OR 0.55, 95% CI 0.41-0.73, P<0.001) without heterogenicity[14].In 5 RCT's reporting pregnancies , more patients treated with LHRHa achieved pregnancy 33 versus 19 women (OR 1.83, 95% CI 1.02-3.28, P=0.041) and in 3 studies reporting disease free survival no difference was observed (HR1.00, 95% CI 0.49-2.04, P=0.939)[14-16]. Thus in situations where oocyte or embryo cryopreservation methods are not feasible in our setting, we then discuss the option for LHRHa suppression during the course of chemotherapy.

Our hope for the future is that we will ultimately eliminate the need for this field onco-fertility through more specific and better innovations that treat and cure the cancer and reduce the unwanted side effects of chemotherapy drugs. But till that time comes, we will continue to develop this field of oncofertility to help our young reproductive age women and men.

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College News

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30th January 2021 was indeed a historic occasion for the College of Obstetricians and Gynaecologists as it marked our maiden foray into the new 'cyber-CPD' era. On short notice, the College embarked on an ambitious project of organizing two online events, the first targeted at specialists while the second was aimed at general practitioners. Not surprisingly, the theme of both these CPD events was Covid related, as this plague has affected possibly everyone, in every imaginable way, for the past 12 months.

Both these events, although put together in record time, went extremely well. In fact, by most standards, it seems to have exceeded our expectations.

The first event on the 30th was a webinar entitled "Covid-19 in Pregnancy: Vaccine?", and had three speakers. The first was none other than Dr Norashikin Abdul Fuad, who is the head of Obstetrics and Gynaecology at Hospital Sungai Buloh, 'ground zero' for 'Covid and Obstetrics' in Malaysia. The other two speakers were Prof Paul Heath and Dr John Latimer, both from the United Kingdom, and have their fingers on the pulse of the international Covid scene. The three invited speakers and three local luminaries made up the discussion panel.

As the chosen speakers and panelists were renowned, the interest generated was nothing short of phenomenal. A total of 400 pax registered their interest in participating within the first 48 hours of opening and just two days before the event, it was clear that the Zoom platform that we had proposed to use was not going to be adequate. Hence the decision was made to also stream the event live on Facebook. In total 1000 pax had access to the CPD event on Zoom, while a remaining participated via Facebook. Since the event, there has been a total of 2500 pax views of the recorded event.

The second event was held the following week on Saturday, 6th February 2021 and was entitled "Covid-19 in Pregnancy: Updates for Primary Care". This was aimed at general practitioners and as expected also generated massive interest. Learning from the first event, a decision was made from the onset to consider live streaming on Facebook. In total, 440 pax were able to access the lectures on the Zoom platform while a further 741 pax did so via Facebook.

The success of these two events has given the new Council impetus to raise the College to the next level. It has become abundantly clear that while there is a need for such CPD events, the College can, if it so desires, also deliver!

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