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EDITORIAL

Achievements in 2017, Promises of 2018

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The year 2017 has been a remarkable one for the Society of Fetal Medicine as well as for medical science in general. Within a short period of time, the Society has emerged as the largest and the most active body of fetal medicine specialists in Asia. We offer our sincere thanks to Dr. Ashok Khurana and his executive team for their outstanding performance. The details of their achievements are described in an accompanying article. Special mention should be made about the launch of the MCAPSV MoMs calculator developed by Dr. Krishna Gopal that can be accessed through the cellphone.

The past year has been an amazing one for reproductive medicine. The results of the long-awaited ASPRE trial were published [1]. Women with singleton pregnancies (n = 26,941) were screened by means of an algorithm that combines maternal factors, mean arterial pressure (MAP), uterine-artery pulsatility index (UTPI), and maternal serum PLGF and PAPP-A at 11–13 weeks' gestation. Those with an estimated risk for preterm PE of > 1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/day) versus placebo from 11 to 14 until 36 weeks' gestation. Preterm PE, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group. The incidence of PE at < 34 weeks was reduced by 82%. It was concluded that treatment with low-dose aspirin in women at high risk for preterm PE reduces substantially the incidence of this disease. However the trial showed that aspirin had no significant effect in reducing the risk of term PE.

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Extreme prematurity is the leading cause of neonatal mortality and morbidity due to organ immaturity, all over the world. Until now, efforts to extend gestation using extracorporeal systems have achieved limited success. Flake et al. reported the development of a system that incorporates a pumpless oxygenator circuit connected to the fetus of a lamb via an umbilical cord interface that is maintained within a closed 'amniotic fluid' circuit that closely reproduces the environment of the womb. Fetal lambs that are developmentally equivalent to the extreme premature human infant were physiologically supported in this extra-uterine device for up to 4 weeks. By creating an artificial placenta that kept premature lamb babies alive for 1 month, the authors have raised the hope that we may have a solution for prematurity in the near future [2].

Small size at birth is associated with perinatal mortality, child morbidity, and adult health risks, all of which are major global health challenges. Nowadays, ultrasound estimation of fetal weight before birth is very widely used in clinical practice. The current reference ranges used worldwide are largely based on single populations from a few high-income countries and are therefore of uncertain general applicability. WHO therefore requested new fetal growth charts based on multiple populations to be made available for general use starting before birth. In all, 1387 healthy women with low-risk pregnancies and unconstrained nutritional and social background from ten countries in Africa, Asia, Europe, and South America were included in a longitudinal study of fetal growth [3]. During pregnancy, repeated ultrasound measurements were used to establish international fetal growth charts for head and abdominal circumference, length of the thigh bone, and fetal weight, estimated using a combination of the three measurements. Fetal growth showed considerable natural variation, differing significantly between countries. Growth

was to a small extent influenced by maternal age, height, weight, and parity, and by fetal sex. Similarly, birth weight varied significantly between countries, even after adjustment for differences in the length of pregnancy. The authors suggest that these WHO charts for growth and estimated fetal weight are more suitable for international use than those commonly applied today. However, the differences between countries, with maternal factors, and with fetal sex mean that these growth charts may need to be adjusted for local clinical use to increase their diagnostic and predictive performance.

Dirty air increasing risk of miscarriage was reported by Mendola and her team [4]. They reviewed data from a long-term study from the U.S. NIH that followed 501 couples between 2005 and 2009. There were 343 couples that achieved pregnancy, but 98 (28%) lost the pregnancy within the first 18 weeks. The findings showed that exposure to ozone appeared to increase risk of pregnancy loss by 12%, and exposure to fine airborne particles raised it by 13%. Although the precise reason for this association is unknown, the study suggested that inflammation and oxidative stress prompted by air pollution could jeopardize a pregnancy in a number of possible ways. It could harm fetal development, interfere with implantation of the fertilized egg in the uterus, or cause problems with development of the placenta. There is a possibility that toxins in air pollution might cross the placenta and directly harm the fetus.

After three decades of research, gene therapy was applied in 2017. (1) A 7 year old boy with life-threatening junctional epidermolysis bullosa had a 4-cm^2 biopsy taken from a non-blistering area of left inguinal region. This was used to establish primary keratinocyte cultures, which were then transduced with a retroviral vector expressing the full-length LAMB3 cDNA. The modified skin was grafted back, making his skin completely normal over a period of 2 years, covering 80% of his entire body surface [5]. The successful outcome of this study paves the way for gene therapy to treat other types of epidermolysis bullosa and provides a blueprint that can be applied to other stem cell-mediated combined ex vivo cell and gene therapies. (2) Patients with hemophilia B were treated with a single injection of an adeno-associated viral vector containing a hyperfunctional factor IX variant gene along with sequences optimizing expression and targeting the liver. All ten participants had sustained mean (± SD) factor IX levels of 33.7 ± 18.5% of the normal value. The annualized bleeding rate and factor IX use were dramatically reduced in treated patients [6]. Hemophilia A is 6× commoner than Hemophilia B, but as the 7-kb factor VIII gene is approximately twice as large as that of factor IX, gene therapy had not been possible so far. However, Rangarajan et al. [7] reported sustained levels of factor VIII after a single infusion of AAV5 with modified hFVIII. Six of seven participants who received the highest dose had normal levels of factor VIII over a period of 20–24 weeks. After 52 weeks, the median level was still 77 IU per deciliter (range 19–164). Despite the high dose of vector, there was no major liver toxicity. These landmark studies by George et al. [6] and Rangarajan et al. are leading the way to a cure for hemophilia. (3) A patient with sickle cell disease was treated with lentiviral vector-mediated addition of an antisickling β-globin gene into autologous hematopoietic stem cells. Adverse events were consistent with busulfan conditioning. Fifteen months after treatment, the level of therapeutic antisickling β-globin remained high (approximately 50% of β-like-globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease [8].

Spinal muscular atrophy is an anterior horn cell disease in which the type 1 disease infants rarely survive beyond 2 years of age. There was no significant treatment until now. Two new treatments developed in 2017 give the hope that a successful treatment may well be in sight. Gene therapy, involving a single intravenous administration of nonreplicating adenovirus, was used in 12 patients [9]. Nine of these who received a high dose were able to sit without support for at least 30 s, and 2 were able to crawl, pull to stand, and walk independently. In the other trial, anti-sense oligonucleotides were administered intrathecally to increase the amount of protein being made by SMN2 gene by preventing the exclusion of exon 7 in SMN2 gene [10]. Of 122 enrolled infants with onset of symptoms at 6 months of age or younger, a significantly larger proportion of infants in the nusinersen group than infants in the control group, achieved motor milestones (41 vs. 0%).

Huntington's disease is a devastating degenerative autosomal disorder with no specific therapy. After over a decade in pre-clinical development, anti-sense oligonucelotides were injected intrathecally in the patients by Tabrizi and colleagues at UCL Institute of Neurology in London [11]. It lowered the level of the toxic disease-causing protein in the nervous system. The drug was safe and well-tolerated. The results of this trial are of ground-breaking importance for Huntington's disease patients and families. This brings us one step closer to treating and potentially preventing this devastating condition. This has been hailed as the biggest breakthrough in neurodegenerative disorders for the past 50 years.

In August 2017, researchers at Oregon Health and Science University, led by Shoukhrat Mitalipov, reported the first known attempt at genetically modifying human embryos in the U.S. They injected CRISPR-Cas into embryos that carried a genetic mutation responsible for an often fatal hereditary cardiomyopathy. CRISPR was able to correct the mutation in about three-quarters of the embryos

[12]. A team from Sun Yat-Sen University in China reported correcting the single-nucleotide mutation that leads to the blood disorder β thalassemia in living human embryos. The base-editing does not cut the DNA when it makes an edit, so it potentially has fewer harmful side effects than classic CRISPR-Cas editing would [13].

India's first uterus transplant was carried out in May 2017 in Pune, from the mother to the 21 year old daughter. A team of 12 doctors at Pune's Galaxy Care Laparoscopy Institute (GCLI) conducted the procedure on a Solapur resident. The surgeons retrieved the uterus using a laparoscopic technique, which is expected to shorten the duration of the procedure [14]. Another womb transplant was carried out a few days later on a 24-year-old woman from Baroda who suffered from Asherman's syndrome (scar tissue in the uterus) and received her mother's womb. The hospital has been preparing for womb transplants over the past few months and recipients were made to undergo ovulation stimulation through IVF. Frozen embryos were implanted in the womb after transplantation for the couple to conceive. The cost of the procedure is around Rs. 7–8 lakh. According to Dr. Puntambekar, the transplantation is not known to harm the recipient or the baby despite the use of anti-rejection drugs (immuno-suppressants) and the multiple surgeries involved. He cited data on kidney transplant patients successfully delivering babies despite being put on immuno-suppressants in support. If the surgery is successful, both the recipients will be able to conceive using in vitro fertilisation (IVF) and have children. Both donor and recipients undergo screening procedure after which the uterus is retrieved and transplanted in the recipient, who undergoes three surgeries. The Maharashtra Directorate of Health Services granted GCLI the license to carry out womb transplantation for 5 years after inspecting its facilities in April this year. The surgical team went to Sweden to learn about the transplantation procedure before practising on human cadavers in Germany and the US. Bangalore-based Milann International Institute for Training and Research in Reproductive Health has also received approval from Indian Council of Medical Research for womb transplantation on two women, but no dates have been announced yet. Womb transplantation was first done in Sweden in 2012 by Mats Brannstrom [15]. He is the first in the world to deliver a baby as a result of a uterus transplant. As of last year, he had delivered five babies from women with donated wombs. Subsequently, uterus transplants have been done in USA. The first birth as a result of a womb transplant in the United States has occurred in Dallas, Texas. For women with a absent uterus or presence of a nonfunctional uterus, transplantation (UTx) has now emerged as the first line therapy for these women, that have traditionally been regarded as unconditionally infertile.

Down's syndrome, also known as trisomy 21, is one of the most common genetic diseases. Researchers from the University of Geneva (UNIGE) and ETH Zurich (ETHZ), Switzerland, published in Nov 2017, the results of analysis of the proteins of individuals with trisomy 21 for the first time: the goal was to improve our understanding of how a supernumerary copy of chromosome 21 could affect human development. Published in the journal Nature Communications [16], the research shows that trisomy 21, far from only affecting the proteins encoded by the chromosome 21 genes, also impacts on the proteins encoded by the genes located on the other chromosomes. In fact, the cells are overwhelmed by the protein surplus generated by the triplicated genes, and cannot regulate the amount of proteins. These results provide new insight into Down's syndrome and its symptoms based on the study of proteins that reveal the different outcomes of an excess of chromosome 21 on cell behaviour.

In recent years, prenatal detection of fetal congenital anomalies has become increasingly more frequent, due to the adoption of routine ultrasound imaging. Simultaneously, advanced genetic testing has evolved demonstrating that an increasing proportion of these anomalies have a genetic cause. Chromosomal microarray analysis (CMA) was added to standard karyotyping as a prenatal diagnostic test increasing the detection rate of clinically significant cytogenetic abnormalities by 6% in cases with a single anomaly (abnormality) and 13% when multiple anomalies were present. Currently, prenatal microarrays have become the test of choice in the presence of ultrasound abnormalities such as congenital heart disease, neural tube defects, oral clefts, and fetuses with increased nuchal translucency. However, even in pregnancies with indication of advanced maternal age, abnormal first trimester screening, or parental anxiety, several reports have found a pathogenic submicroscopic abnormality in 0.5–2% of such pregnancies, a much higher frequency than the 1/800 population risk of Down syndrome [17]. Therefore, many have suggested that CMA should become the test of choice for *all* women undergoing invasive testing.

This year fetal genomic (whole exome) sequencing (WES) as a diagnostic test for women with pregnancies complicated by major fetal congenital anomalies increased the detection rate of genetic findings by 10–30%. The Prenatal Assessment of Genomes and Exomes (PAGE) study aims to sequence 1000 fetus-parent trios in pregnancies complicated by unexplained fetal abnormalities to determine the diagnostic yield in different categories of clinical findings to inform policy for implementation in the UK National Health Service. Currently, the study has recruited over 600 families with sequencing results available in 256. Overall, WES found the genetic cause of abnormalities in 6% of cases. The highest yield (16%) was

in those with multiple congenital anomalies, with lower yields in fetuses with isolated anomalies or increased nuchal translucency [18].

2018 promises to be a bigger year for science and fetal medicine. We are going to hear more about CRISPR-cas9 technology to correct gene defects. The non-invasive prenatal diagnosis of aneuploidies and micro-deletions will be extended with a number of companies offering diagnosis of single gene disorders through non-invasive technology. Quick whole genome sequencing of the newborn pioneered by Kingsmore, is likely to become even more popular and will definitely be used to a greater extent for fetal diagnosis. Fetal Imaging will continue to improve and innovate as part of the digital revolution with better visualization of the fetus and its internal organs. However, fetal ultrasound requires more skill and training than just pushing a button. Those that make the effort to master the modality will reap rich rewards for their patients. The practice of ultrasound offers the imager the possibility of direct patient contact to guide the examination, which is unique to ultrasound and represents the essence of fetal medicine. The Society of Fetal Medicine will do its utmost to provide opportunities for members to improve and hone their skills in fetal ultrasonography and fetal interventions, and also impart the new knowledge in obstetrics and genetics to better serve our patients.

We are happy to announce that the journal will continue to be published by Springer-Nature. The number of pages per issue has been increased to 60–65. The readers will find that the journal with a new cover will include many new features. All articles will be screened for clinical relevance by the two editors-in-chief (Dr. Ashok Khurana and Dr. I. C. Verma). We hope the readers will like future copies of the journal. We look forward to their feedback so that the journal can be improved even further.

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