J. Fetal Med. (March 2015) 2:1–4
DOI 10.1007/s40556-015-0045-z

EDITORIAL

Advancing Horizons in Fetal Medicine

Ishwar C. Verma[1]

Received: 6 July 2015 / Accepted: 7 July 2015 / Published online: 17 July 2015

The four issues of 2014 of the Journal of Fetal Medicine have just rolled out. It has been an exciting and tough year for us at the Editorial Board. We struggled through the process of having sufficient articles to publish. But at long last, we feel we have turned the corner, and now there is a steady stream of articles being submitted for publication. The Society of Fetal Medicine, on the other hand, is flourishing, and the membership is ever expanding. This is largely through the untiring and enthusiastic efforts of our Secretary Dr Ashok Khurana. A large number of cities in India (Mumbai, Kochi, Bangalore, Hyderabad, Jodhpur, Ludhiana, Patiala, Faridkot, Agra, Aurangabad, and Kochi have opened branches of the Society of Fetal Medicine, and have organized numerous regional continuing medical educational programs. This is testimony to the popularity of fetal medicine in the country, as well as, to the influence of our Society. Given that there are about 26 million births per year in India, fetal medicine will continue to flourish for years to come. What is amazing is that in spite of this huge number of births, the IVF clinics are flourishing at an even faster pace than fetal medicine and obstetrics. This emphasizes the strong desire of the couples to have a baby in our society. Fortunately, this desire is matched by the fervent wish of the couples to have a normal baby. Couples who have a pregnancy from conception through IVF, making the baby very precious, are willing to undergo tests to ensure normality of the baby.

We would like to examine briefly the advances that have occurred in the field of fetal medicine in 2014. No doubt the single most advance, which has shaken the obstetricians and fetal medicine specialists, is the noninvasive prenatal testing of chromosomal disorders. The Journal had its share of articles on this topic. Cuckle emphasized the changing scene brought on by the NIPT technology [1]. Benn provided a good overview of the subject [2], while Verma [3] and Dash and colleagues [4] presented their experience with this technology in India. They reiterated that NIPT is still a screening test, and needs confirmation of a positive result with an invasive test. Secondly, it is not a good option if the nuchal translucency in the first trimester or nuchal fold thickness in the second trimester is increased, or there are ultrasound abnormalities, or there is history of miscarriages or abnormalities in past pregnancies. In all these instances, it would be good to have a full fetal karyotype, and also have fetal DNA for further studies once the five aneuploidies are excluded. Numerous papers on the use of NIPT in high-risk pregnancies have been published in 2014. Recently, papers have appeared demonstrating its utility in the low-risk population as well [5, 6]. Once the cost comes down, it would be routinely used in all pregnancies. Recently, there have been two excellent papers on the experience in detecting microdeletions [7, 8] Those using massively parallel sequencing technology claim they would be able to detect all deletions and duplications in the genome, and this advance in technology is awaited with baited breath. We also look forward, with excitement, to the application of this technology for the diagnosis of single-gene disorders. What is heartening to see is the establishment of this technology right in India by one company, to avoid the dispatch of samples abroad. More companies are likely to follow suit. Hopefully, this will also lead to lowering of the cost of the test, and the turn-around time for the reports. Lo et al. have recently described how the massively parallel sequencing technology has been used to determine the fetal genome, methylome, and transcriptome [9].

✉ Ishwar C. Verma
jfm200@yahoo.co.in

[1] Center of Medical Genetics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110060, India

Cytogenetic prenatal diagnosis has, for long, been dependent on karyotyping, which requires time-consuming cell culturing, has a limited resolution (5–10 Mb), and is dependent on optimal harvesting and chromosome staining conditions. Nowadays, genomic microarray technology allows whole-genome testing at a higher resolution and it can be applied to uncultured fetal material, allowing shorter reporting times when compared with classical cytogenetic techniques [10]. Microarrays have a higher diagnostic yield—3 % of cases, regardless of referral indication; ~9 % of cases with multiple ultrasound anomalies; ~5.6 % of cases with isolated ultrasound anomalies; and ~0.5–2 % in cases without ultrasound anomalies [10]. Many laboratories abroad have given up classical karyotyping, replacing it with whole genome microarrays. Once the cost comes down this is likely to be the case in India too. Then the indications of karyotyping in fetal tissues would remain as (i) trisomy 13 or 21 detected by QF PCR, FISH, NIPD, or array testing, in order to differentiate between heritable and nonheritable Down and Patau syndrome; (ii) in case of normal array result, when one parent is a carrier of a balanced chromosomal aberration, in order to investigate whether the fetus inherited the familial chromosomal aberration; (iii) in case of abnormal array results, to specify the chromosomal abnormality (e.g., duplication, insertion, marker chromosome, unbalanced translocation; (iv) to determine the recurrence risk by metaphase FISH studies in case of submicroscopic aberrations.

The year saw the publication, in the Journal, of the guidelines of anomalies scan in the second trimester [11], rule-of-three second trimester scan popularized by Suresh [12], the first trimester scan to detect aneuploidies using nuchal translucency, nasal bone, ductus venosus, tricuspid valve, and facial angle [13], utility of prefrontal space [14], and the correct method to record nuchal translucency [15]. The Society has been active in developing more guidelines for ultrasonologists and fetal medicine specialists and we hope to publish these in 2015. In practice, it is frustrating that many ultrasonologists still do not record the nuchal translucency correctly, leading to endless worries for the concerned parents. The Society of Fetal Medicine, through the efforts of our Secretary, Dr Khurana, has been conducting courses and educational exercises, across the country, to teach the ultrasonologists the correct method of analyzing nuchal translucency. Dr Suresh in South India is also spearheading this movement at his center and has been recognized for conducting courses in this by the Fetal Medicine Foundation in London. Dr Kaul in Delhi and Dr Radhakrishnan in Bangalore are engaged in similar activities. We wish them success.

We had articles emphasizing the value of obtaining at least a radiograph of the skeleton after fetal demise [16, 17], how it aids in providing a specific diagnosis of fetal skeletal dysplasias, and use of autopsy to find the etiology of fetal limb anomalies [18]. Fetal autopsies are still the gold standard in the diagnosis of fetal anomalies. We plan to bring out a special issue on fetal autopsies with contributions from USA and India. The issue will be edited by Dr Raj Kapur and Dr Sunil Jaiman. Genetic studies are an important component of fetal autopsies, not only in cases of congenital malformations, but also in unexplained intrauterine death and sudden unexpected death in infancy [19]. We also published articles on management of Rh isoimmunization [20], growth restriction [21] and prenatal diagnosis of lysosomal storage disorders [22].

Mention may be made of some advances in fetal imaging in recent years. In 2010, Chaoui and Nicolaides [23] published their paper entitled "From nuchal translucency to intracranial translucency: towards the early detection of spina bifida". They showed that in normal fetuses the fourth cerebral ventricle presents as an intracranial translucency (IT) parallel to the nuchal translucency, while in fetuses with open spina bifida, there is absence or loss of the IT. Recently, Volpe et al. [24] pointed out that between the border of the fourth ventricle and cistern, normal fetuses always have three spaces and two lines parallel to the occipital bone, between the sphenoid bone anteriorly and the occipital bone itself, posteriorly. The first line consists of the posterior border of the brainstem and the anterior border of the fourth ventricle, and the second line dividing the developing fourth ventricle and cisterna magna, presumably, represents the choroid plexus of the fourth ventricle. The absence of one of these posterior brain spaces suggests the diagnosis of spina bifida, cephalocele, Dandy–Walker malformation, or chromosomal abnormalities. Another good marker of spina bifida in the first trimester (BPD/transverse abdominal diameter $\leq$1) was described by Simon and colleagues [25]. Another advance has been the use of fetal 'black bone' MRI using susceptibility-weighted imaging for better demonstration of the mineralized skeleton [26].

The three-dimensional (3D) high-definition (HD) ultrasound has resulted in remarkable progress in visualization of early embryos and fetuses in sonoembryology. The new technology of HDlive assesses both, structural and functional, developments in the first trimester with greater reliably than two-dimensional (2D) ultrasound. The 3D technology humanizes the fetus, and enables detailed observation of the fetal face in the first trimester (e.g., of Down syndrome and holoprosencephaly), as well as low-set ears and finger/toe abnormalities [27]. Ultrasound detection rates of facial clefting have been reported to be as low as 21 %–30 %, this is set to change with the use of 3D technology [28]. We are happy to announce that the Society, in collaboration with Fetal Imaging Academy in

Bangalore, through the efforts of Dr Ashok Khurana, will be conducting a unique online course in 3D ultrasonography using the latest, cutting-edge technology. This training will include all about 3D ultrasonography, and show how this has impacted clinical decision making. During the training program, delegates will have access to video lectures and can send three volume submissions for review by the faculty.

Fetal cardiac medicine has evolved considerably over the past two decades, predominantly in response to advances in imaging technology and innovations in therapies. The diagnosis of cardiac disease in the fetus is mostly made with ultrasound; however, new technologies, including 3D and 4D echocardiography, magnetic resonance imaging, and fetal electrocardiography and magneto-cardiography, are available. Medical and interventional treatments for select diseases and strategies for delivery room care enable stabilization of high-risk fetuses and contribute to improved outcomes. A recent statement by the American Heart Association highlights what is currently known and presents recommendations on the basis of evidence and experience [29].

The advent of NIPT has coincided with the use of massively parallel sequencing in molecular diagnosis. This has resulted in the opportunity to provide prenatal diagnosis in cases that, hitherto, was impossible. The explosion of new genomic technologies continues to offer great benefits [30]. However, each technology needs critical assessment prior to adoption in a clinical setting [9] For example, molecular genetics of three common fetal neurological abnormalities (holoprosencephaly, lissencephaly, and agenesis of the corpus callosum) have been published [31]. These should assist greatly in prenatal diagnosis and perinatal management.

Fetal surgery has also seen great advances, three of which need mention [32, 33]. In utero repair of myelomeningocele has been shown to be better than operating after delivery. However, this is unlikely to be adopted in India, as fetuses with spina bifida are terminated. Management of twin-to-twin transfusions by use of laser has been highly successful abroad, and we are happy that a number of centers have started offering this intervention in India, leading to the survival of infants that were being lost earlier. Tracheal occlusion for diaphragmatic hernia is still, currently, being investigated as the next promising step in fetal intervention, and would vastly improve the prognosis in diaphragmatic hernia.

Lastly, in utero transplantation (IUT) with stem cells could cure affected fetuses [34], but so far, in humans, successful IUT using allogeneic hematopoietic stem cells (HSCs), has been limited to fetuses with severe immunologic defects; and more recently, IUT with allogeneic mesenchymal stem cell transplantation, has improved phenotype in osteogenesis imperfecta. Amniotic fluid stem (AFS) cells have been isolated and characterized in humans and are a potential source of cells for therapeutic applications prenatally or postnatally. Gene transfer to the cells with long-term transgenic protein expression is feasible. The results obtained in animal models have been encouraging, and bring personalized tissue engineering for prenatal treatment of genetic disorders closer to the clinic.

References

1. Cuckle H. Steering the course between optimal policies and practical restraints. J Fetal Med. 2014;1:3–5.
2. Benn P. Noninvasive prenatal testing using cell-free DNA in maternal circulation. J Fetal Med. 2014;1:107–11.
3. Verma IC. Noninvasive prenatal testing: the Indian perspective. J Fetal Med. 2014;1:113–8.
4. Dash P, Puri RD, Kotecha U, et al. Using noninvasive prenatal testing for aneuploidies in a developing country: lessons learnt. J Fetal Med. 2014;1:131–5.
5. Bianchi DW, Parker RL, Wentworth J, et al. CARE Study Group. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014;370(9):799–808.
6. Norton ME, Jacobsson B, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015;372:1589–97.
7. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. Am J Obstet Gynecol. 2015;212:332.e1-9.
8. Wardrop J, Jesiolowski J, Dharajiya N, et al. Updated clinical experience of trisomy 16 and 22, and microdeletion detection by non-invasive prenatal testing (NIPT). Abstract number 364. Presented at 2015 ACMG Annual Clinical Genetics, March 25, 2015. Salt Lake City. Utah. USA.
9. Wong AI, Lo YM. Noninvasive fetal genomic, methylomic, and transcriptomic analyses using maternal plasma and clinical implications. Trends Mol Med. 2015;21(2):98–108.
10. Srebniak MI, van Opstal D, Joosten M, et al. Whole-genome array as a first-line cytogenetic test in prenatal diagnosis. Ultrasound Obstet Gynecol. 2015;45:363–72.
11. Khurana A, Makhija B, Deka D, et al. Society of Fetal Medicine: practice guidelines for the second trimester anomalies scan. J Fetal Med. 2014;1:11–5.
12. Seshadri S, Suresh I. The second trimester obstetric scan ($7 + 3 = 10$): a rational approach (including the "rule of three"). J Fetal Med. 2014;1:59–73.
13. Thummalakunta P, Panditi S. Approach to screening for aneuploidy in first trimester. J Fetal Med. 2014;1:175–9.
14. Suskin B, Roe A-M, Bajaj K. Utility of prefronatal space ratio to screen for trisomy 21 in a racially diverse population: a pilot study. J Fetal Med. 2014;1:25–7.
15. Ratha C, Khurana A. "First things first": images for a proper nuchal translucency in the first trimester $11 - 13 + 6$ weeks scan. J Fetal Med. 2014;1:55–7.
16. Deka D, Naha M, Dadhwal V, et al. At least an infantogram if not perinatal autopsy. J Fetal Med. 2014;1:33–9.
17. Puri RD, Verma IC. The role of radiographs in fetal autopsy. J Fetal Med. 2014;1:7–9.
18. Kotecha UH, Puri RD, Dash P, et al. Need for fetal autopsy and genetic diagnosis in fetal limb anomalies. J Fetal Med. 2014;1:151–7.
19. Scheimberg I. The genetic autopsy. Curr Opin Pediatr. 2013;25(6):659–65.

20. Agarwal K, Rana A, Ravi AK, et al. Treatment and prevention of Rh isoimmunization. J Fetal Med. 2014;1:81–8.
21. Gujral K, Nayar S. Current trends in management of fetal growth restriction. J Fetal Med. 2014;1:125–9.
22. Sheth J, Mistry M, Sheth F, et al. Prenatal diagnosis of lysosomal storage disorders by enzymes study using chorionic villus and amniotic fluid. J Fetal Med. 2014;1:17–24.
23. Chaoui R, Nicolaides KH. From nuchal translucency to intracranial translucency: towards the early detection of spina bifida. Ultrasound Obstet Gynecol. 2010;35:133–8.
24. Volpe P, Muto B, Passamont U, et al. Abnormal sonographic appearance of posterior brain at 11–14 weeks and fetal outcome. Prenat Diagn. 2015;35:717–23.
25. Simon EG, Arthuis CJ, Haddad G, et al. Biparietal/transverse abdominal diameter ratio $\leq$ 1: potential marker for open spina bifida at 11–13-week scan. Ultrasound Obstet Gynecol. 2015;45:267–72.
26. Robinson AJ, Blaser S, Vladimirov A, et al. Foetal "black bone" MRI: utility in assessment of the foetal spine. Br J Radiol. 2015;88:20140496.
27. Pooh RK, Kurjak A. Novel application of three-dimensional HDlive imaging in prenatal diagnosis from the first trimester. J Perinat Med. 2015;43:147–58.
28. Hassan WA, Lees CC. Facial cleft detected: is the palate normal? Best Pract Res Clin Obstet Gynaecol. 2014;28:379–89.
29. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014;129(21):2183–242 **(Erratum in Circulation. 2014 May 27;129(21):e512.)**.
30. Wapner RJ, Levy B. The impact of new genomic technologies in reproductive medicine. Discov Med. 2014;17(96):313–8.
31. Huang J, Wah IY, Pooh RK, et al. Molecular genetics in fetal neurology. Semin Fetal Neonatal Med. 2012;17:341–6.
32. Moise KJ Jr. The history of fetal therapy. Am J Perinatol. 2014;31:557–66.
33. Vrecenak JD, Flake AW. Fetal surgical intervention: progress and perspectives. Pediatr Surg Int. 2013;29:407–17.
34. Ramachandra DL, Shaw SS, Shangaris P, et al. In utero therapy for congenital disorders using amniotic fluid stem cells. Front Pharmacol. 2014;5:270.