Preface

Aris T Papageorghiou

Few subjects capture the imagination more than how humans grow and develop. The apparent biological simplicity of two cells coming together belies the enormously complex and highly regulated changes that will result in a fetus and newborn. The link between our physical development into what makes us who we are, with the behavioral, cognitive, and emotional changes we experience during our lifetime, are of course shaped by innumerable factors – our genes, our environment, education and cultural milieu. But it is also increasingly clear that our short "start in life" – just 280 or so days of intra-uterine existence - has a profound effect on our subsequent chances of healthy development.

As clinicians, monitoring growth is an essential part of care and aims to determine if there are growth abnormalities that may signify underlying nutritional disorders or disease; and to take steps to reduce related morbidity and mortality. Given the enormity of the subject area, it is natural to break this up into epochs of development, and in this issue leading experts consolidate the latest evidence regarding diagnosis and management of aberrations of *fetal* growth. Nevertheless, it must be remembered at all times that human development is a continuum. Recent progress towards a fully integrative approach to monitoring growth and development from early pregnancy to school age globally means this is now within our grasp[1].

The fact that sub-optimal fetal growth places the baby at increased risk of stillbirth and fetal distress in labour has been shown in numerous studies; in his thought-provoking article Bob Silver explains the link between the fetus that is small for gestational age (below a certain percentile of size) and stillbirth. He examines this link in light of recent relevant data that suggest that there may be some bias at play; this is because there is weight loss of a baby between death in utero and being weighed at birth; and also due to the time-lag between these two events. He concludes that here is no doubt that there remains an association, probably causative, between poor fetal growth and adverse outcome; but that such bias may artificially strengthen this association. Clearly further detailed research is needed to understand the implications of this.

What is also clear is that estimating the size of the fetus prenatally is a prerequisite for the diagnosis of growth aberrations; for the most part, the tool used for this is ultrasound. The excellent article by Neil O'Gorman and Laurent Salomon explains how such assessment should best be undertaken; it includes the crucial aspect of gestational age estimation, without which interpretation of appropriateness of size for gestation is impossible. The chapter also covers concepts such as using interval fetal growth; but also novel imaging modalities such as 3D ultrasound and MRI. Despite these advances in imaging the fetus, Gordon Smith makes the important point that current evidence is not conclusive as to whether universal late pregnancy ultrasound does more harm or more good; the data are suggestive, but ultimately inconclusive. It must also be said that in large parts of the world ultrasound is not available meaning that gestational age estimation and fetal assessment has to be undertaken clinically. Sikolia Wanyonyi and Steve Mutiso share their experience on how this impacts diagnosis and management of growth restriction in low resource setting and what strategies are required to improve this situation. A particular scenario of increased risk of growth abnormalities is in twin pregnancy. Rosie Townsend and Asma Khalil share their insights into the specific issues concerning how diagnosis and particular management differ in this setting.

One of the principles of screening that Wilson and Jungner defined in 1968, is that there should be an accepted treatment [2]. In the context of fetal growth restriction, currently this is indicated early birth of the baby; Aamod Nawathe and Anna David review all current preventative or treatment modalities that may ameliorate growth restriction due to poor placental function, and point out the most promising opportunities.

The manifestation of growth restriction in the fetus is a series adaptions to the in-utero environment through endocrine, metabolic and cardiovascular changes. These are described in outstanding detail by Karel Marsal. It is through measurement of these physiological parameters using ultrasound (but also increasingly using biomarkers) that allows us to fine tune our management. These measurements help the clinician, who is faced with a number of questions: what is the cause of the growth pattern seen? when should I review this patient? and when should I deliver the poorly growing baby? Ahmed Baschat's description of a uniform approach to management, shows how outcomes

can be improved in both early and late onset growth restriction by carefully balancing the benefits of advancing gestational age versus the ever impending risks of stillbirth. Once the baby is born, there is a critical opportunity for postnatal growth and development and the chapter by Bianca Carducci and Zulfi Bhutta outlines how specialist care of such high-risk newborns is necessary in order to overcome particular challenges, such as those of poor thermoregulation, how to provide correct nutrition and indeed how to monitor growth postnatally.

Finally there is an important chapter on how we can use consensus. A great deal of evidence can be gained in medicine by data synthesis. In very simple terms, many small studies can be amalgamated to reach larger samples and more robust estimates. But this is often difficult to achieve as many studies use different definitions, measurements and outcomes. Take as an example the commonly used term “intrauterine growth restriction”, often defined as the inability of the fetus to achieve its genetic growth potential. But as genetic growth potential is not currently a definable characteristic, how can we define its absence? For this reason, consensus, based on the opinion of many individual contributors, can take the field forward - although it must always be remembered that the fetus is not taking part in these consensus procedures. Sanne Gordijn, Irene Beune and Wessel Ganzevoort, give us their view on the advantages and pitfalls of this approach.

It has been a privilege to work with the world’s foremost experts on this issue of Best Practice & Research: Clinical Obstetrics & Gynaecology. The end result is a series of articles of remarkable quality. It should keep you busy reading this journal from cover to cover, and I am confident you will enjoy reading it as much as I enjoyed editing it!

References

(1) Villar J, Papageorghiou AT, Pang R, Salomon LJ, Langer A, Victora C, Purwar M, Chumlea C, Qingqing W, Scherjon SA, Barros FC, Carvalho M, Altman DG, Giuliani F, Bertino E, Jaffer YA, Cheikh Ismail L, Ohuma EO, Lambert A, Noble JA, Gravett MG, Bhutta ZA, Kennedy SH. Monitoring human growth and development: a continuum from the womb to the classroom. Am J Obstet Gynecol. 2015 Oct;213(4):494-9.

(2) Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf

Acknowledgment

Aris T. Papageorghiou is supported by the Oxford Partnership Comprehensive Biomedical Research Centre, with funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme.

Other funding streams

Feb 2018 – present	Computer Assisted LOw-cost Point-of-care UltraSound (CALOPUS): Co Investigator, my role is working between clinical and engineering faculties to develop low cost automated ultrasound solutions.	EPSRC/NIHR
Nov 2017-present	PRECISE: PREgnancy Care Integrating translational Science Everywhere network: Co Investigator, my role is developing a low cost automated gestational age assessment tool using ultrasound.	RCUK Global Challenges Research Fund
April 2017 – present	BRC3 Imaging Theme: Collaborator, working in a multidisciplinary team to develop automated quality control solutions for third trimester ultrasound,	NIHR
Nov 2016 – present	PULSE: Co-Investigator, examining perception of ultrasonographers when undertaking these examinations.	ERC
Oct 2016-present	What is the value of undertaking a study to determine the clinical & cost effectiveness of late pregnancy ultrasound to prevent adverse perinatal outcome in nulliparous women? Co-Investigator.	NIHR - Health Technology Assessment
July 2016 – present	SONO-EX: PI, working with industry to achieve automated 3D ultrasound for basic fetal biometry.	Philips Healthcare
Apr 2014 – present	Safer pre-natal diagnosis using cell free DNA in maternal blood test: PI, developing cell free DNA testing (also known as the IONA study).	Premaitha Health
Apr 2014-Sep 2017	A randomised controlled trial of sildenafil therapy for severe, early-onset intrauterine growth restriction, co-investigator	NIHR - Efficacy and Mechanism Evaluation
Mar 2014-Mar 2016	Automating quality assessment of B-mode ultrasound scans (AQABUS): PI, clinical lead	EPSRC / Technology Strategy Board
April 2013 – present	Fetal heart rate data: PI, automating antenatal heart rate analysis.	Huntleigh
Dec 2011-2015	Computerised fetal heart rate analysis in labour to assist timely diagnosis of fetal distress and prevent birth asphyxia: PI.	Action Medical Research
Mar 2011-2021	International Fetal and Newborn Growth Consortium: INTERBIO-21st: Co-Investigator, in charge of all ultrasound and obstetric aspects in this large multinational study.	Bill & Melinda Gates foundation
Mar 2011-Oct 2017	International Fetal and Newborn Growth Consortium: INTERGROWTH-21st: Collaborator, in charge of all ultrasound and obstetric aspects in this large multinational study.	Bill & Melinda Gates foundation