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Original article

Standardisation of neonatal clinical practice

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The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) is a large-scale, population-based, multicentre project involving health institutions from eight geographically diverse countries, which aims to assess fetal, newborn and preterm growth under optimal conditions. Given the multicentre nature of the project and the expected number of preterm births, it is vital that all centres follow the same standardised clinical care protocols to assess and manage preterm infants, so as to ensure maximum validity of the resulting standards as indicators of growth and nutrition with minimal confounding. Moreover, it is well known that evidence-based clinical practice guidelines can reduce the delivery of inappropriate care and support the introduction of new knowledge into clinical practice. The INTERGROWTH-21st Neonatal Group produced an operations manual, which reflects the consensus reached by members of the group regarding standardised definitions of neonatal morbidities and the minimum standards of care to be provided by all centres taking part in the project. The operational definitions and summary management protocols were developed by consensus through a Delphi process based on systematic reviews of relevant guidelines and management protocols by authoritative bodies. This paper describes the process of developing the *Basic Neonatal Care Manual*, as well as the morbidity definitions and standardised neonatal care protocols applied across all the INTERGROWTH-21st participating centres. Finally, thoughts about implementation strategies are presented.

Keywords Neonatal care protocols, neonatal guidelines, neonatal morbidity definitions, preterm growth, preterm infants, standards of care.

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Introduction

Of the 8.8 million deaths of children under five in 2008, 41% (3.6 million) occurred within the neonatal period and almost 12% (1.03 million, uncertainty range 0.72–1.22 million) were related to prematurity.[1] Data on the global burden of prematurity also point to a considerable, yet unspecified, burden of morbidity.[2] It is estimated that, in 2005, preterm births accounted for almost 13 million births worldwide; 85% (11 million) of these occurred in Africa and Asia.[3] Where good-quality trend data are available, these also suggest that the rates of preterm birth are rising. Given the increasing evidence that size at birth and subsequent postnatal growth velocity may be critically related to long-term neurological and metabolic outcomes, the development of normative standards is an important step in targeting interventions. The development and utilisation of growth charts for preterm infants is a necessary step towards appropriate evaluation of their postnatal growth in clinical practice.

The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) is a large-scale, population-based, multicentre project involving health institutions from eight geographically diverse coun-

tries. The project aims to assess fetal, newborn and preterm growth under optimal conditions, in a manner similar to that adopted by the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS).[4] The INTERGROWTH-21st Project has three major components, which were designed to create: (1) longitudinally derived, prescriptive, international, fetal growth standards using both clinical and ultrasound measures; (2) preterm, postnatal growth standards for those infants born at $\geq 26^{+0}$ but $<37^{+0}$ weeks of gestation in the longitudinal cohort; and (3) birthweight-for-gestational-age standards derived from all newborns delivering at the study sites over an approximately 12 month period.[5]

Given the multicentre nature of the project and the expected number of preterm births, it was vital that all centres followed the same, standardised, clinical care protocols to assess and manage preterm infants, so as to ensure maximum validity of the resulting standards as indicators of growth and nutrition. All infants in the Preterm Postnatal Follow-up Study (PPFS) are monitored for the first 8 months of life using the same protocol and set of anthropometric measurements as in MGRS.[6] Although the standardisation of anthropometric measurements is a central element of the project, given the importance of optimising care for preterm infants, it was considered essential that all the participating institutions used common definitions of neonatal morbidities and followed standardised neonatal care protocols. The implementation of common clinical practice guidelines is an important prerequisite in defining the context of nutrition and care for preterm infants.[7]

Development of the basic neonatal care manual

The INTERGROWTH-21st Neonatal Group produced an operations manual,[5] which reflects the consensus reached by members of the group regarding the definitions of neonatal morbidities and the minimum standards of care to be provided by all centres taking part in the INTERGROWTH-21st Project. The operational definitions and summary management protocols were developed following a systematic process of literature review and best fit of relevant guidelines. This process was undertaken by collaborating neonatologists and overseen by a core group led by Prof. ZA Bhutta. Specific areas were reviewed by group members and a systematic search of existing management protocols in participating centres was undertaken. All subgroups were encouraged to develop key definitions and relevant management recommendations for implementation. All core definitions and protocols were presented and consensus was reached when the Neonatal Group met in Oxford in July 2009. The agreed protocols and operational definitions were then developed into a *Basic Neonatal Care Manual* and implemented after a pilot phase. Finally, in April 2011, the manual was reviewed during the Neonatal Group's second meeting. Figure 1 summarises the overall process undertaken.

This paper describes the consensus-based components of the manual, including the morbidity definitions and standardised neonatal care protocols that were implemented uniformly across all participating INTERGROWTH-21st centres.

Summary of neonatal morbidities and management recommendations

In this section, a brief overview of the main topics in the manual is given. For the sake of brevity, not all the sections are summarised here, and only the main respiratory and neurological conditions are described in detail. Summary paragraphs about nutrition, thermoregulation, anaemia requiring transfusion, hyperbilirubinaemia and sepsis are also included.

Administration of antenatal steroids to women at risk of preterm delivery

The group reviewed the evidence for the use of antenatal steroids to prevent prematurity-associated, respiratory distress syndrome. According to the most recent guidelines[8,9] and established findings from a systematic review,[10] a single course of steroids should be administered as a routine preventive intervention to all women, between 24 and 34 weeks of gestation, who are at risk of preterm delivery within 7 days, and to all women with premature rupture of membranes at <32 weeks of gestation. Repeated doses must be used with caution as a recent meta-analysis showed

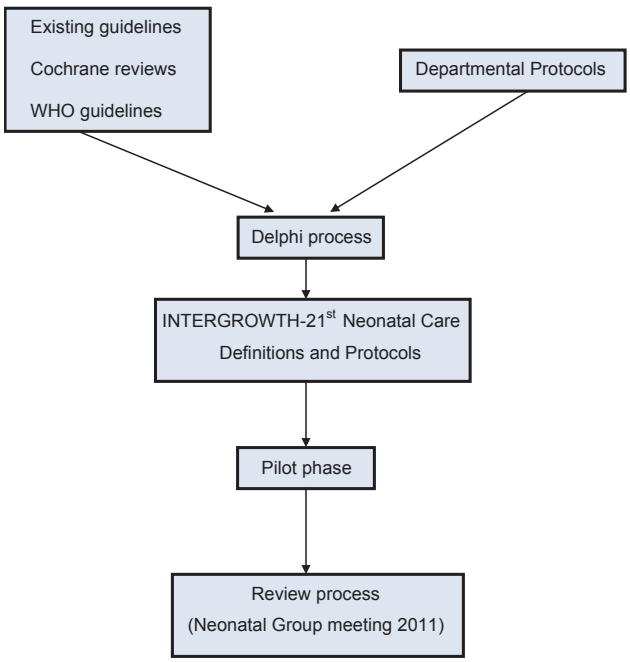

Figure 1. Preparation of the neonatal care manual.

significantly impaired fetal growth compared with placebo,[11] which may lead to long-term neurodevelopmental consequences. The most recent review of the evidence[12] suggests that antenatal steroids administered to at-risk mothers decrease neonatal mortality among preterm infants (<36 weeks of gestation) by 31% (relative risk [RR] 0.69; 95% confidence interval [95% CI] 0.58–0.81). The meta-analysis of four randomised controlled trials from middle-income countries also indicates a 53% mortality reduction (RR 0.47; 95% CI 0.35–0.64) and 37% morbidity reduction (RR 0.63; 95% CI 0.49–0.81). In addition, recent data suggest that the use of antenatal steroids is both effective and safe in women with preterm premature rupture of membranes plus chorioamnionitis and no increased risk of complications.[13] A standard protocol of administration of antenatal steroids was, therefore, agreed for implementation across the INTERGROWTH-21st sites.

Respiratory tract disorders in the early neonatal period

There are several morbidities commonly observed in the preterm neonate, including:

- Transient Tachypnoea of Newborn—a parenchymal lung disorder characterised by pulmonary oedema resulting from delayed resorption and clearance of fetal alveolar fluid. Onset usually within 2 hours of delivery. X-ray characteristics: increased lung volumes, prominent vascular markings and fluid in the interlobar fissure.[14]
- Respiratory Distress Syndrome—diagnosed if each of the following are present:
  - Requires oxygen at 6 hours of life continuing to age 24 hours
  - Demonstrates clinical features within first 24 hours
  - Has need for respiratory support up to age 24 hours, AND
  - Has an abnormal chest X-ray within first 24 hours consistent with surfactant deficiency, OR
  - Has received surfactant therapy within the first 24 hours of life.[15,16]
- Meconium Aspiration Syndrome—respiratory distress in an infant born through meconium-stained amniotic fluid, whose symptoms cannot be otherwise explained. Can be complicated by respiratory failure, pulmonary air leaks and persistent pulmonary hypertension.[14,17]

The Neonatal Group also considered additional conditions and agreed on a set of standard management protocols described in the manual.[5] As an illustration, the respiratory distress syndrome management protocol is summarised in Table 1.[14,18,19]

Birth asphyxia

Birth asphyxia remains a major killer in the neonatal period[20] and can also be a significant burden in preterm infants with high rates of mortality and sequelae.[21] Given the need for diagnostic specificity, we recommended the definition of birth asphyxia in an infant satisfying at least one of the following criteria: Apgar score ≤5 at 10 minutes; mechanical ventilation or resuscitation at 10 minutes; cord pH <7.1 or an arterial pH <7.1 or base deficit ≥12 within 60 minutes of birth; evidence of encephalopathy according to Sarnat staging.[22–25]

Thermoregulation

Appropriate thermoregulation is key to the care and growth of preterm infants. In order to ensure standard management, the group considered a number of thresholds[24,26] and agreed on the following management protocols.

At delivery

The delivery room or operating theatre is always too cold for a very-low-birthweight newborn. Hence, the baby should be thoroughly dried, wrapped, resuscitated and moved to a warmer environment, as soon as possible.

Maintaining adequate thermoregulation for the preterm infant in the immediate newborn period is dependent on:

- Adequate environmental temperature in delivery room >25°C
- Use of warmers for infants <29 weeks of gestation or if prolonged resuscitation is required
- Occlusive plastic wrapping at delivery for all infants <32 weeks of gestation
- Hats and swaddling
- Maintaining temperature stability during stabilisation in neonatal intensive care unit (NICU).

Incubator care

A closed incubator provides an infant with high ambient temperature while allowing attendants to work at a lower, more comfortable temperature. Recommended temperatures and humidity grades for each gestational age at birth are provided in the manual. These settings also depend on whether the infant is clothed or naked, and on the infant's weight and postnatal age.

Weaning to crib

When the infant's temperature is maintained within a normal range at low incubator temperatures (i.e. <34°C) and heater output of <50%, then thermal aides can be slowly weaned. They should be removed one at a time with effectiveness assessed over 6–8 hours before making further changes.

Initiation of feeding

The goal of the guideline, which is consistent with recent reviews of the literature,[27,28] is to promote exclusive breast-

Table 1. Management recommendations for respiratory distress syndrome (RDS)

Clinical condition	Management recommendations
Respiratory distress syndrome	Administration of surfactant: Surfactant should be given to infants with RDS as soon as possible after intubation irrespective of antenatal steroid exposure or gestational age and prophylactic surfactant replacement should be considered for extremely preterm infants at high risk of RDS, especially if they have not been exposed to antenatal steroids. Use of nasal Continuous Positive Airway Pressure (nCPAP): Indicated for babies ≥27 weeks of gestation with low risk of significant RDS or mild RDS on X-ray.Initial settings: 4–5 (max 7–8) cm H_2O, fraction of inspired oxygen (FiO_2) 0.4–0.5, flow 6–8 l/minute. Monitoring: Respiratory rate, work of breathing, colour/O_2 saturation, perfusion, blood pressure, chest expansion and pneumothorax on chest X-ray, blood gas, air leak syndrome. Consider intubation during nCPAP: FiO_2 >0.6 or more than one apnoeic episode per hour requiring stimulation, or if work of breathing is significant. Extubation to CPAP: Infant active, exhibits spontaneous respiratory effort and is not in respiratory failure (FiO_2 <50%, PCO_2 <60 mmHg on low ventilator settings). Weaning from CPAP: Wean to CPAP of 5 cm H_2O and discontinue when infant is stable with FiO_2 <0.30; recommence CPAP if apnoea or FiO_2 increases.

feeding of the preterm infant at the time of hospital discharge. With this aim, the preferred feed is mother's own milk (from breast or expressed), followed by donor human milk, and then preterm formula.

A starting volume of approximately 80 ml/kg/day is indicated, with daily increases of 10–20 ml/kg to a maximum of approximately 160–180 ml/kg/day by the end of the first week of life. For infants <32 weeks of gestation, small amounts of trophic feeds (5–10 ml/kg/day) can be introduced on the first day of life unless illness prevents this. Milk can be given via a nasogastric tube either intermittently or continuously. Although theoretical benefits and risks of each method have been proposed, actual clinical benefits and risks of the two methods cannot be reliably discerned from the limited information available from the randomised controlled trials to date.[29] Therefore, no specific recommendation is provided regarding this issue.

The indicated duration of exclusive breastfeeding is 6 months in low-birthweight infants, accompanied by adequate supplementation. Multicomponent fortifiers may be useful in lower gestational age infants. Indications given in the manual about feed volumes, progression and human milk supplementation are mostly based on WHO recommendations.[27] Table 2 summarises recommendations regarding daily enteral nutrients.

Table 2. Recommended daily enteral nutrients for preterm infants >1000 g at birth

Nutrient	Birth to 7 days	Period after birth stabilisation to term
Energy, kJ/kg (kcal/kg)	292–334 (70–80)	438–563 (105–135)
Protein, g/kg	1.0–3.0	3.0–3.6
Fat, g/kg	0.5–3.6	4.5–6.8
Carbohydrate, g/kg	5.0–20.0	7.5–15.5

Other common neonatal morbidities

Respiratory tract disorders in the late neonatal period

• Apnoea of Prematurity—clinically significant apnoea in infants is defined as breathing pauses that last for >20 seconds, or for >10 seconds if associated with bradycardia or oxygen desaturation[14]

• Bronchopulmonary Dysplasia—chronic supplemental oxygen needs for >28 days OR chronic supplemental oxygen needs at either 36 weeks postmenstrual age or discharge from hospital, whichever comes first.[14]

Table 3 summarises the apnoea of prematurity management protocol.

Hyperbilirubinaemia in preterm and low-birthweight babies

Hyperbilirubinaemia is very common and usually benign in term and late preterm (i.e. 35–36 weeks of gestation) newborns.[30] Critical hyperbilirubinaemia is uncommon but has the potential for causing long-term neurological impairment.

Clinicians should ensure that all infants are routinely monitored clinically for the development of jaundice. Measurement of total serum bilirubin and/or total cutaneous bilirubin should be performed in every newborn who develops jaundice in the first 24 hours of life; further monitoring of total serum bilirubin levels depends on the first bilirubin value, the age of the infant and the evolution of jaundice.[31]

Table 3. Management recommendations for apnoea of prematurity

Clinical condition	Management recommendations
Apnoea of prematurity	General measures: tactile stimulation, correct anaemia, maintain normal body temperature; look for electrolyte imbalance, intraventricular haemorrhage, signs or symptoms of sepsis, patent ductus arteriosus, necrotising enterocolitis and gastro-oesophageal reflux, and treat it accordingly. Specific treatment: theophylline or caffeine, depending on availability and neonatologist's preference. *Aminophylline:* 5–6 mg/kg orally or intravenously (infused over 15–30 minutes) as a loading dose, followed by a maintenance dose of 2 mg/kg starting 12 hours after the loading dose. *Caffeine:* 20 mg of caffeine citrate (10 mg of caffeine base) orally or intravenously as a loading dose, followed by a maintenance dose of 2.5–5 mg/kg/day as a single dose of caffeine base. Therapy discontinuation: gestational age >37 weeks with weight of 1800–2000 g, or if the infant has been apnoea free for 7 days. Failure of drug therapy: use nasal Continuous Positive Airway Pressure (nCPAP) at a rate of 2–4 cm H_2O or high-flow nasal cannula at 1–2 l/minute and continue administration of the drug. If apnoea and bradycardia cannot be controlled by drug therapy or nCPAP, consider mechanical ventilation with low pressures.

The basic pathophysiology of jaundice is the same in term and preterm babies but lower gestational age infants are at higher risk of developing hyperbilirubinaemia and, therefore, require close surveillance and monitoring. Total serum bilirubin thresholds for intervention vary in term, late preterm and preterm (<35 weeks of gestation) newborns.

The American Academy of Pediatrics (AAP) has a guideline for newborns ≥35 weeks of gestation, but the management of more preterm infants is still a grey zone; hence, many institutions have their own guidelines. Those adopted in this study are based on the AAP guidelines and confined to newborns ≥35 weeks of gestation.[31] Following the recent publication of the National Institute for Health and Care Excellence recommendations,[32] a subcommittee of the Neonatal Group discussed whether or not to update the manual; however, the decision was made to retain the AAP guideline as the common protocol among the participating centres.

Sepsis

There are various operational definitions of neonatal sepsis, many dictated by a combination of blood culture positivity and clinical features.[33–36] For the INTERGROWTH-21st Project, neonatal sepsis was defined as a clinical syndrome of systemic illness accompanied by bacteraemia occurring in the first month of life. Late onset sepsis was defined as one or more positive blood cultures obtained after 3 days of age from infants with clinical features of sepsis. However, as culture-positive sepsis is relatively rare, a physician-documented episode of sepsis sufficed for comparative purposes.

In the manual, guidelines are provided regarding specific antibiotic management and supportive care although it is recognised that these are contextual to the prevalent organisms and spectrum of infections. First-line antibiotics indicated in the manual are ampicillin (50 mg/kg every 12 hours if aged ≤7 days, but every 8 hours if aged >7 days) and gentamicin (5 mg/kg once daily if aged ≤7 days, but 7.5 mg/kg once daily if aged >7 days).

In nosocomial sepsis, the flora of the local NICU must be considered and first-line antibiotic choice must vary depending on resistance patterns.[37]

Anaemia requiring transfusion

The group could not reach consensus on a common definition of anaemia. The threshold for treatment of anaemia of prematurity was then decided on the basis of criteria developed by the US and Canadian collaborative study, namely to transfuse infants with a volume of 15 ml/kg, administered over 2–3 hours.[38]

Neurological complications

Hypoxic ischaemic encephalopathy

Hypoxic ischaemic encephalopathy is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures.

The cornerstone of treatment is supportive care and careful maintenance of systemic homeostasis[39] even if the management of each asphyxiated baby is individualised. Given the importance of hypoxic ischaemic encephalopathy aftercare, guidelines are provided in the manual about appropriate fluid and electrolyte management, timing and dosage of vasopressors to maintain adequate perfusion and treatment of seizures if needed, with general recommenda-

tions about gastrointestinal care and when to start enteral nutrition, based on recent evidence.[40]

Screening for intraventricular haemorrhage and periventricular leukomalacia

Based on a review of the literature and expert opinion, routine screening for intraventricular haemorrhage or periventricular leukomalacia is recommended only in newborns <30 weeks of gestation, after the first 7–14 days of life and thereafter at 36–40 weeks of gestation or just before discharge.[41] However, we anticipated that this would be an uncommon occurrence within the context of the INTERGROWTH-21st Project.

Continuation of feeding for the preterm infant

As anticipated in the section above on initiation of feeding, the goal is breastfeeding promotion for the preterm infant at the time of hospital discharge. In addition, the ideal duration of exclusive breastfeeding is 6 months in low-birthweight infants, accompanied by adequate supplementation[27] (e.g. vitamin D 400 IU/day if birthweight <1500 g).

The issue of exclusive breastfeeding at discharge was thoroughly discussed at the last Neonatal Group Meeting, in April 2011, for its relevance to the INTERGROWTH-21st Project. We concluded that it is vital for the participating centres to implement exclusive breastfeeding strategies for all the infants enrolled. The first steps are to increase awareness and educate all healthcare professionals about the benefits of human milk and breastfeeding support in the mothers of preterm infants. Thereafter, establishing a strong relationship between the family and the local investigator is recommended, and the investigator should be available for breastfeeding counselling and encouragement.

To monitor implementation, each participating centre is asked to report its breastfeeding rates; the data and any barriers to implementation are then discussed on a regular basis.

Evidence-based implementation of the basic neonatal care manual and protocols

To assist care providers with decisions about appropriate health care in the clinical circumstances described above, it was important not only to develop valid recommendations based on current evidence, but also to ensure the implementation of the evidence-based recommendations. According to *A Guideline Developer's Handbook*, published by the Scottish Intercollegiate Guidelines Network,[42] the main external barriers to implementation are structural factors such as financial disincentives, organisational issues (e.g. lack of facilities or equipment), local standards of care not in line with desired practice and individual factors (e.g. knowledge, attitude and skills).

Specific efforts were made in the context of the INTERGROWTH-21st Project to overcome such external barriers to implementation. First, we ensured there was adequate financial support for, and standardisation of, locally qualified human resources. Second, the availability of facilities and equipment was checked before the project started. Third, during the initial implementation of the project, the Neonatal Group confirmed that local practices were not in conflict with our recommendations by asking a neonatologist (AH) to assist the Chair (ZAB) in obtaining information about local capacity and standards of care. Finally, successful implementation depends upon the local quality of human resources and ability to follow standardised guidelines; although this is always challenging, there are measures in place to ensure ready communication and coordination between the Neonatal Group and the centres.

During the April 2011 meeting, the group discussed issues pertaining to implementation, such as the breastfeeding strategy described above. Subsequently, a neonatologist (FG) was put in charge of implementing the manual and coordinating PPFS within the centres. Implementation included translation of the manual as required (e.g. Italy, China), and identification of a local neonatologist as the PPFS coordinator, who could present the manual to the medical and nursing staff in each NICU. A comparison between local NICU protocols and the guidelines presented in the manual was then performed and issues were discussed with the PPFS coordinator. In this respect, it is relevant to say that the manual describes a basic level of care and does not represent a strict protocol; so, local higher level of care (e.g. sophisticated ventilation, surfactant therapy, selective hypothermia for asphyxiated newborns) was readily accepted.

Conclusions

Building prescriptive standards requires that the population selected has the best potential for growth, and receives adequate standardised nutrition and evidence-based clinical care. As regards nutrition, the goal is the promotion of exclusive breastfeeding of the preterm infant at the time of hospital discharge, ideally continued exclusively for 6 months. In addition, all preterm infants should receive standardised, evidence-based, medical care across all the neonatal units involved and the study follow-up clinics.[43] This can be achieved only through adequate coordination among the local neonatologists in the participating centres and by following the operations manual for clinical practice developed by the Neonatal Group.[5] The crucial importance of sharing and implementing the manual lies mainly in the promotion of exclusive breastfeeding, which also involves counselling families, and in the standardisation of clinical care among units in different geographical areas, both of which are essential from a global perspective.[44]

Although restricted to the study groups themselves, the process of agreeing on common definitions and protocols for the care of newborns, including preterm infants, was unique and informative. Despite diverse backgrounds and contexts spanning five continents, investigators were able to agree upon common protocols and implement them. The INTERGROWTH-21st *Basic Neonatal Care Manual* presents up-to-date clinical guidelines based on reviews of the published evidence and is therefore a valuable tool to improve standards of clinical care in developing countries. It should be recognised that these represent aspirational guidelines and would need to be adapted by countries to suit specific needs in district and referral hospitals. However, at least in one instance in Pakistan, the manual has been used to develop national guidelines for hospital-based care for newborns in the district.[45] With increasing interest in newborn care in developing countries at various levels of care, this manual should complement developing guidelines by agencies such as WHO for the hospital care of children and newborns.[46]

Disclosure of interests

The authors declare that there are no conflicts of interest.

Contribution to authorship

ZAB and FG wrote the manuscript and all the authors read and approved the final version.

Details of ethics approval

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee 'C' (reference: 08/H0606/139) and the research ethics committees of the individual participating institutions and corresponding health authorities where the Project was implemented.

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A full list of Members of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and its Committees appears in the preliminary pages of this supplement. ■

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