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Original article

Implementation of the INTERGROWTH-21st Project in the UK

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There are approximately 10 000 births per year in the county of Oxfordshire in the UK, which is one of the two European sites for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project. The samples for both components of the project – the Fetal Growth Longitudinal Study (FGLS) and Newborn Cross-Sectional Study (NCSS) – were drawn from the John Radcliffe Hospital, a major university hospital with a large regional role that covers more than 75% of deliveries in the county. Special activities to encourage participation in this population included the formation of a research coalition to streamline recruitment in the Maternity Unit and the distribution of study information leaflets to women using the hospital's antenatal care service. This was a demanding project and several challenges were overcome to reach recruitment targets and to maintain high standards of data quality. Amongst the major challenges for FGLS at this study site was the level of ineligibility because of maternal age, smoking and body mass index (BMI) ≥ 30. The major challenge for the NCSS field teams was to ensure that all anthropometric data were collected before the early discharge of uncomplicated deliveries, often within 6 hours of birth. It is evident from our experience in implementing this project that, when large-scale clinical studies are meticulously planned and avoid major disruption to routine clinical care, they are well received by hospital staff and can contribute to the improvement of the overall standard of clinical care.

Keywords Fetal growth, INTERGROWTH-21st, nutrition, standards.

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Introduction

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, in a manner similar to that adopted by the WHO Multicentre Growth Reference Study (MGRS).[1] 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.[2]

The county of Oxfordshire in the UK is one of the two European sites for the INTERGROWTH-21st Project. Oxfordshire has a population of 639 700, which includes a large proportion of young, middle-class, well-educated, professional families.[3] Thirty-seven per cent of the Oxfordshire population hold a university degree, 16% higher than the national average.[4]

Almost 10 000 births occur in Oxfordshire per year. During the process of selecting health institutions for the INTERGROWTH-21st Project, a census was taken of all

Table 1. Delivery services in Oxfordshire (2009)

Hospital name	Deliveries
John Radcliffe Hospital, Oxford (includes a Midwifery-led Unit)	6895
Horton General Hospital, Banbury	1779
Chipping Norton Midwifery-led Unit	143
Wantage Midwifery-led Unit	96
Wallingford	241
Total	9154

hospitals in Oxfordshire in which babies are delivered (Table 1). The Maternity Unit selected was that of the John Radcliffe Hospital, Oxford, a major university hospital with a large regional role that covers 75.3% of deliveries in Oxfordshire (Figures 1 and 2). The hospital also houses the University of Oxford's Nuffield Department of Obstetrics & Gynaecology, which is where the INTERGROWTH-21st Project Coordinating Unit is located.

The general pregnant population served by the John Radcliffe Hospital is at low risk of fetal growth impairment, which is reflected in the hospital's delivery statistics (Table 2). In 2008, the mean birthweight was 3334 g; the low birthweight and perinatal mortality rates were 6% and 8% respectively. In addition, 99% of mothers delivering in the unit have completed secondary school or university level education.

Figure 1. Location of Oxfordshire. H: hospital participating in the INTERGROWTH-21st Project; h: maternity unit not participating in the INTERGROWTH-21st Project.

Preparatory activities

Ethical approval for the project was obtained from Oxfordshire Research Ethics Committee C in December 2008. A study team for the Fetal Growth Longitudinal Study (FGLS) was recruited in early 2009 comprising a research midwife, two experienced ultrasonographers and a data manager. The ultrasonographers and data manager attended centralised training sessions in April 2009,[5,6] prior to the launch of FGLS in May 2009 (Figure 3). Access to rooms within the Outpatient Department for screening and scanning purposes was negotiated with the hospital management in early 2009.

Two teams of five anthropometrists were formed to collect data for the Newborn Cross-Sectional Study (NCSS): one for measuring newborns admitted to the Neonatal Intensive Care Unit (NICU) and another for measuring healthy newborns on the postnatal wards. A senior nurse practitioner coordinated the anthropometrists, and a neonatologist was responsible for supervising the completion of data collection forms. The anthropometry teams were trained by the lead anthropometrist, who attended central training in Nairobi, Kenya, as described elsewhere in this supplement.[7,8]

FGLS implementation

During the preparatory phase of the study, a number of research groups operating in the hospital formed a coalition known as the Oxford Safer Pregnancy Alliance (OSPREA), which was intended to streamline the recruitment of pregnant women for research purposes. A letter was devised by the OSPREA team and sent out to all newly pregnant women, outlining the various studies being conducted. The new system meant that women would only be approached by one research midwife during their visit to the hospital; this midwife would assess their eligibility for *all* the studies being conducted, thereby reducing the risks of duplication on the part of the research midwives and of overwhelming women with information. The new OSPREA recruitment process served to increase the total number of women involved in research in the unit.

Screening logistics

In the UK, antenatal care is usually shared between the hospital and midwives/general practitioners in the community. However, most antenatal visits occur in the community, with selected hospital visits at 12 and 20 weeks and again near term. Standard blood tests at booking (including aneuploidy screening) and a 20-week anomaly scan are offered to all women. For this reason, screening for FGLS

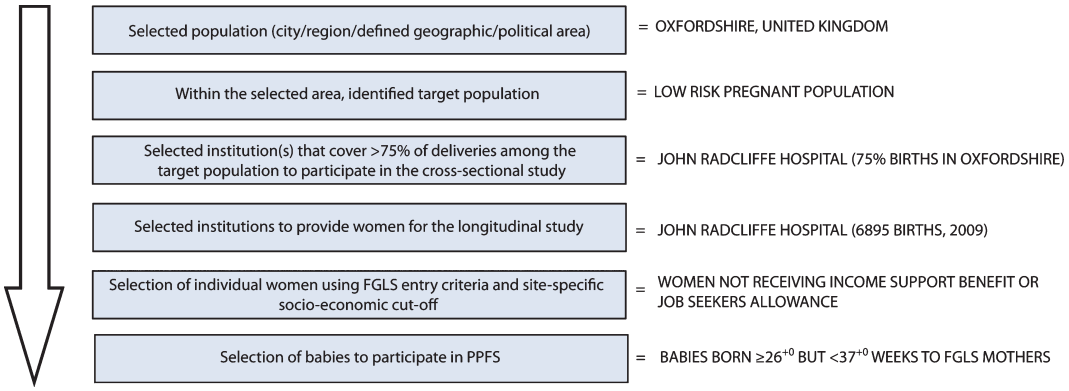

Figure 2. Summary of population-based sampling strategy in Oxford, UK.

Table 2. John Radcliffe Hospital data

Indicator of population at low risk of fetal growth impairment	Value	Protocol requirement met
Low birthweight rate (%)	6	Yes
Perinatal mortality rate (per 1000 live births)	0.8	Yes
Mean birthweight (g)	3334	Yes
Maternal secondary education (%)	>99	Yes
Altitude (m above sea-level)	55	Yes

was carried out in the Outpatient Ultrasound Department, where women from the county usually come for their first ultrasound scan at approximately 12 weeks of gestation.

Women who met the FGLS screening criteria were selected from the general pregnant population served by the John Radcliffe Hospital. The screening criteria identified pregnant women at low risk for all factors known to affect fetal growth and development, including socio-economic constraints. The receipt of State benefits (Jobseeker's Allowance or Income Support) was used as a proxy for low socio-economic status in this population.

During an initial piloting phase, women attending the Outpatient Clinic were screened using the FGLS eligibility criteria. Of the 41 women screened, only three were eligible, that is a potential recruitment rate of 7%. Major reasons for exclusion were: maternal age ($n = 15$), smoking ($n = 6$) and uncertain last menstrual period (LMP) ($n = 6$). This raised some concern about the study site's ability to meet the recruitment targets. However, after consulting with staff in the antenatal clinic, it transpired that the women involved in the pilot study were particularly high risk and atypical of those attending the unit. Another piloting exercise was therefore conducted to refine the recruitment process. This time, 100 women were screened, with a more favourable 22% eligibility rate.

The recruiting midwife was granted access to the hospital's computer appointment system, which allowed rapid

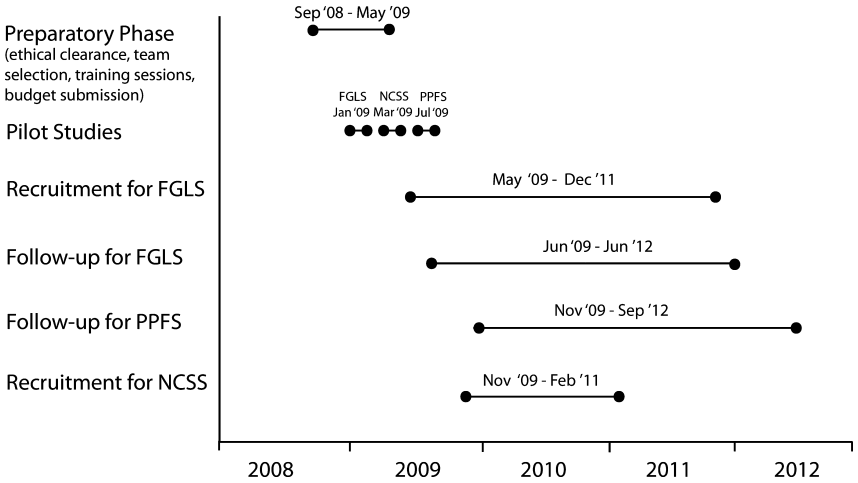

Figure 3. Project timeline in UK.

'pre-screening' of all women attending the clinic each morning. This meant that only potentially eligible women were approached, thereby further streamlining the recruitment process. Occasionally, women heard about the study from friends/relatives and volunteered themselves for screening. Potentially eligible women were approached by the research midwife, who briefed them about the study and took verbal consent to begin the formal screening process. The midwife completed the screening interview in a quiet room and referred the women for an ultrasound dating scan to confirm the gestational age. Women with confirmed eligibility who were willing to participate were given a consent form to read at home; it was then signed at their next appointment, 4–6 weeks later.

By far the most common reason for ineligibility in the UK was maternal age > 35 years. Other common reasons were unwillingness to consent, maternal smoking and maternal body mass index (BMI) ≥ 30. These findings were consistent with the results from the INTERGROWTH-21st sites in the USA and Italy. Although recruitment in the UK during the first 3 months of the study was lower than expected, the rate soon increased as more women heard about the study. From August 2009 onwards, the monthly target of 25 enrolments was consistently met. It was important not to recruit more than 25 women per month as this would have placed cumulative pressure on the ultrasound scanning team as the study progressed.

Follow-up logistics

Women enrolled in the study attended ultrasound scan appointments at intervals of 5 ± 1 weeks from 14^{+0} weeks onwards until delivery, but not beyond 42^{+0} weeks. The scans were performed by dedicated, trained ultrasonographers, using a Philips HD-9 ultrasound machine (Philips Ultrasound, Bothell, WA, USA). The same commercially available machine was used by ultrasonographers at all the INTERGROWTH-21st participating centres to ensure reliable measurements, to facilitate technical support and data transfer, and to ensure that a balance was struck between various criteria, example cost, imaging quality, functionality etc.

Several strategies were adopted to ensure a high retention rate throughout the study. First, women were not discouraged from bringing their relatives or children to the appointment (this is not usually possible at routine clinical scans). Second, at each scan appointment, women were given two- and three-dimensional photographs of their baby to take home, if possible. Third, the study team endeavoured to provide a highly personalised service, by giving antenatal advice and making referrals to appropriate hospital clinics if necessary: for example, the external cephalic version clinic or the antenatal physiotherapist. Once a woman began her follow-up scans, it was very unusual for her to withdraw, except in a few cases of relocation.

At the last scan appointment before delivery, women were thanked for their participation and given a bag and baby T-shirt printed with the study logo. They were also encouraged to email a photograph of their baby wearing this T-shirt for the study website. Women and their partners were frequently reminded of the importance of notifying the research team as soon as the baby was born, so that the anthropometry team could take measurements within 12 hours. A telephone number was provided that was linked to a 24-hour answering machine service, which was checked three to four times a day by the anthropometry team. For the very small number of FGLS babies born outside the hospital, parents were asked to bring the baby to the John Radcliffe Hospital for measurement as soon as possible after the delivery.

Preterm follow-up logistics

All babies born at $\geq 26^{+0}$ but $<37^{+0}$ weeks to mothers in the FGLS cohort were entered into the Preterm Postnatal Follow-up Study (PPFS), which was overseen in Oxford by an experienced nurse practitioner, with the assistance of several trained anthropometrists working in the hospital's NICU.

Soon after the preterm birth, parents were briefed about the study requirements and follow-up schedule.[3] The initial anthropometric measurements were completed during hospital admission. Follow-up appointments took place in the Special Care Baby Unit until the baby left the hospital. After discharge, follow-up appointments were arranged with the parents. For maximum convenience, attempts were made to coordinate visits with the infant's routine clinical care appointments wherever possible.

Email and text message reminders were sent out the day before each appointment and parents quickly became familiar with the follow-up schedule. The regularity of visits enabled the anthropometric team to develop strong relationships with the parents. Parents were also given access to free parking, feeding advice and resuscitation training.

Data entry and quality control

Clinical data gathered using the FGLS and PPFS data collection forms were entered into the online system within 3 days of being collected, so that timely queries could take place if necessary. All forms were checked visually for missing values before entry and quality control checks by the data manager took place regularly.

NCSS implementation

The cross-sectional study was presented to senior midwives and other maternity ward staff at the John Radcliffe Hospital, 1 month prior to the onset of the study in November

2009 (Figure 3). Information leaflets were made available in the three maternity wards, the areas in which mothers are transferred after delivery, including the Midwifery-led Unit, and the observational area in which mothers remain for close observation after caesarean section or a traumatic delivery. Written consent from the mothers was not required as the hospital adopted the anthropometric protocol as routine practice for the duration of the study. We hope that this protocol will be retained, representing an important practical contribution of clinical research to improving the direct care of infants.

The initial training and standardisation session for the anthropometry team was conducted in November 2009 and was overseen by lead anthropometrists from the INTERGROWTH-21st Anthropometry Group. Subsequent standardisation sessions were conducted every 3 months, led by the local lead anthropometrist according to the Anthropometry Protocol.[7]

Data collection, entry and quality control

All mothers admitted for delivery at the John Radcliffe Hospital were included in NCSS between November 2009 and February 2011. The data collection, quality control and data management activities were organised as shown in Table 3.

Table 3. Newborn Cross-Sectional Study (NCSS) data collection, entry and quality control activities

Anthropometric data collection
Collect list of the deliveries over the past 24 hours
Visit maternity wards, delivery suite and observation area twice daily
Complete forms with the measurements and return to coordinating person
Data collection and quality control
Complete forms with maternal data and baby outcomes
Update list of FGLS women with their expected date of delivery, registering the corresponding NCSS number after delivery
Visual checks of forms for completeness, consistency and accuracy
Forward completed forms for data entry
Prepare periodic report on the rate of measured and missed babies, FGLS deliveries, etc. sent to the coordinating team
Inform the local Principal Investigator about general study needs
Data management
Enter data into the on-line database
Raise queries on missing or inaccurate fields
Enter corrected data
Store completed and entered forms

FGLS, Fetal Growth Longitudinal Study.

In the UK, it is the norm for low-risk mothers to be discharged soon after delivery, sometimes within 6 hours of giving birth. All efforts were made to minimise the number of babies who did not have anthropometric measurements taken. Strict rotas for the anthropometry team were imposed, covering every day of the week, and measurement shifts took place twice daily, once in the morning and again mid-afternoon. Despite this careful planning, the initial rate of missed babies in the first month of the study equated to 21% of all deliveries. To overcome this problem, the morning measurement session was moved to an hour earlier and the anthropometrists were instructed not only to visit the maternity wards and observation area, but also the labour ward, where they measured the babies whose mothers were likely to be discharged early. A bleep number and an answering machine were set up in the INTERGROWTH-21st office; staff on the labour ward and the Midwifery-led Unit were asked to inform the anthropometry team of any early discharges. As a result of these measures, there was a sharp decrease in the percentage of missed babies, which remained relatively stable over the remainder of the study at around 5% (Figure 4). For babies that were missed, the delivery room birthweight was obtained from the medical record and flagged on the database as having come from this source.

Babies that were admitted to the NICU presented another challenge. Although the head circumference of these babies was always easily measured, the issue of weighing and measuring the length of these very sick, mechanically ventilated babies was difficult. In these cases, the in-built scales in the incubators were used instead of the study scales. Efforts were made to calibrate the incubator and study scales in the same way. With regard to length, it was sometimes necessary to postpone the measurement of sick or preterm newborns up to the point of clinical stability. Major malformations (e.g. severe spina bifida), which would also prevent the measurements being taken, rarely occurred.

The final problem experienced by the data collection team related to values missing from the medical records or unobtainable details. For example, not all maternal heights

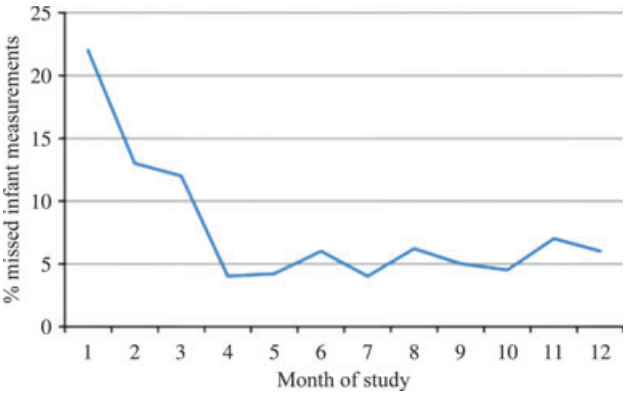

Figure 4. Percentage of missed infant measurements.

were obtained using study equipment because of maternal refusal, post-caesarean section recovery or early discharge. However, these values were taken where possible from the medical records and flagged on the database as coming from this source. The overall percentage of missing values was very low.

Conclusions and lessons learned

For FGLS, after initial uncertainty about the ability of the Oxford site to meet the target recruitment rate, the number of women enrolled in the study reached the target set by the protocol, an average of 25 per month. This was achieved thanks to careful and effective planning, and close teamwork among the research midwives. Families taking part in FGLS and PPFS often developed a close relationship with the study team during the course of the follow-up period. The internationally important nature of the study was stressed from the beginning, and this led to a high level of commitment, with most women reluctant to miss any scans.

NCSS was a demanding study and several challenges were overcome to obtain a low rate of missed babies and to maintain high standards of data quality. Moreover, liaison with the hospital staff and fitting in with the daily hospital routines were essential, but not always easy to achieve. A highly committed team that communicated on a daily basis served to resolve quickly any problems that arose, to avoid errors and to maintain an efficient system. It is evident from our experience in implementing this project that, when large-scale clinical studies are meticulously planned and avoid major disruption to routine clinical care, they are well received and supported by hospital staff, and can contribute to improve the overall standard of clinical care.

Disclosure of interests

None.

Contribution to authorship

FR, HEK and LCI wrote the manuscript and all authors read and approved the final version.

Details of ethics approval

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee (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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