The GROW customised fetal growth model: background, principles, validation and application

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Contents

Acknowledgments

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Declaration

This thesis is submitted to the University of Warwick in support of an application for the degree of Doctor of Philosophy by Published Work. It has been composed by Andre Francis under the supervision of Professors Jason Gardosi and Siobhan Quenby and has not been submitted in any previous application for any degree.

Tables and figures list

Abbreviations list

AC, abdominal circumference
BMI, body mass index
BPD, biparietal diameter
BW, birthweight
CV, coefficient of variation
DESIGN, a randomised controlled trial to evaluate the GAP programme
EFW, estimated fetal weight
FGR, fetal growth restriction (retardation)
FL, femur length
FW, fetal weight
GAP, growth assessment protocol
GROW, gestation-related optimal weight
HC, head circumference
ICD-10/11, International Classification of Diseases, versions 10/11
IG-21, INTERGROWTH-21st project
IUGR, intra-uterine growth restriction
LGA, large for gestational age
LMP, last menstrual period
NICHD, National Institute of Child Health and Human Development (USA)
OR, odds ratio
P, percentile (e.g. P10, P50)
PAR, population attributable risk
PGF, proportional growth function
PMR, perinatal mortality rate
RCT, randomised controlled trial
RR, relative risk
SGA, small for gestational age
TOW, term optimal weight
WHO, World Health Organisation

Summary

In this paper I set out my application for a PhD by published works.

First, I present the background and need that led to this work. While the assessment of fetal growth is an essential part of clinical care, there were substantial limitations in traditional models' growth charts in clinical practice; namely, their 'one size fits all' approach, with no allowance for individual variation.

I next describe the innovative concepts applied to address this problem, and outline the principles that led to the 'gestation-related optimal weight' (GROW) standard: adjustment for individual variation, optimisation to exclude pathological influences, and the application of a fetal rather than a birthweight standard to delineate normal growth. Using these principles, GROW can produce personal antenatal charts, centred on each baby's individual growth potential.

I then selected eight publications to illustrate the validation and application of these principles, highlighting for each: objective, my contribution, key findings and impact.

The first three studies dealt with validation of the GROW principle through comparison with various population based standards, and show that the customised approach performs better at confirming normal growth and identifying growth-restriction-related pregnancy outcomes.

The next five studies present various applications of this standard to enhance our understanding of risk factors for fetal growth restriction, stillbirth, perinatal morbidity and cerebral palsy. A key finding (publication 7) was that risk can be reduced by improved antenatal recognition of fetal growth problems, helping to stimulate and focus health service initiatives on prevention. The series culminates in a study describing the results of implementation of a surveillance programme including GROW charts across three English health service regions, leading to a significant reduction in stillbirth rates.

I believe my contribution to these studies and others over more than 25 years has supported the development and international recognition of the GROW standard.

Chapter 1. Introduction

For over 25 years I have been the statistician at the heart of 40 peer-reviewed clinical papers and 25 abstracts for posters and presentations. My responsibility in all of them as senior statistician was collaboration with source data providers, data integrity, analysis, production and presentation of derived statistics, tables and charts and, through discussion with clinical co-authors, the interpretation of results.

In this thesis I intend to demonstrate how the approach of the 'gestation-related optimal weight' (GROW) [1,2] standard addresses the limitations in the use of traditional 'population-based' models to assess fetal growth using their 'one size fits all' approach.

GROW produces unique individualised and customised growth charts and birthweight centiles which integrate physiological variables proven to influence baby weight and thus account for heterogeneity in the population. The model can provide a vast combination of charts based on a basic set of maternal characteristics, predicting the expected optimal weight.

The model also defines the trajectory by which this optimal endpoint is to be reached during intrauterine growth, through its fetal weight [3] based proportionality formula which converts the expected term weight to gestation related optimal weights. Thereby preterm weights in pregnancies ending prematurely can be assessed against a standard based on normal outcome, term pregnancies.

I present how this technique has been shown to be more sensitive in detecting adverse outcomes overall and within subgroups of the population, and therefore can identify significantly more SGA (small for gestational age) cases at increased risk of perinatal mortality and morbidity than its population-based counterparts. This improves clinical confidence through the reduced misclassification when using customised charts.

Once the workings and the underlying evidence are considered, the only remaining limitation of the model may be that in busy clinics, details of maternal characteristics may not all be collected to adjust the chart for each pregnancy. However this has not been a big obstacle in clinical practice once the method is implemented with training. In the UK, three quarters of pregnancies have a customised chart produced routinely at the beginning of pregnancy.

Chapter 2. Population growth models

> *"We all construct worldviews that give us a sense of meaning. Mostly it is about belonging to a group and having a sense of identity and purpose."*
>
> *Carmen Lawrence (1948 -)*

2.1 Introduction

So-called population models portray each potential member as having a fixed weight at a given gestation, often stratified by sex. The advantage of this form of growth model is the convenience and simplicity of its technique and use but this 'one size fits all' modelling strategy has various practical limitations which are discussed in this chapter.

'Descriptive' (or reference) models are samples from a pregnancy population containing all subjects, including those at high risk for FGR (fetal growth restriction) or overgrowth, whereas 'prescriptive' models aim to represent a normative standard which exclude cases with known risk factors for FGR. Hoftiezer et al [4] compared these two types of model in the Netherlands to show that a prescriptive standard could improve identification of SGA cases at risk of adverse neonatal events. A significant prescriptive international example is Villar et al [5], under the umbrella of the INTERGROWTH-21st project (IG-21) [6], which selected low-risk, well-nourished mothers with uncomplicated pregnancies. Birthweight references both local, such as Carr-Hill [7] (Aberdeen), or national, for example Kallen [8] (Sweden), will necessarily include varying degrees of pathology, particularly preterm births, which will often have been affected by growth restriction preceding delivery described by Gardosi [9]. This was also shown by Zeitlin et al [10] and Regev et al [11], who further demonstrated the association of SGA premature infants in Israel with morbidity and mortality [12].

Before the established use of ultrasound, early studies to investigate growth were based solely on LMP (last menstrual period)-dated birthweights, the unreliability of which had been reported [13–15] and a particular consequence of this is the artificial flattening of weights at term described by Wilcox et al [16] and contrasting with their own ultrasound-dated birthweight (BW) reference. Alexander [17] later presented a large, LMP-dated USA reference where gestation, known to be compromised, was adjusted using a birthweight standard, but some flattening can still be seen in their presented charts.

2.2 Birthweight growth models

Birthweight (BW) curves are a de facto, cross-sectional record of baby weights at delivery and their primary purpose is a reference that clinicians can use to measure the effects of growth and manage postnatal care. Although early papers often blurred the distinction between fetal weight and birthweight, many authors acknowledged problems in representing intrauterine growth derived from birthweights [18] most notably at preterm gestations. The importance of a BW centile for clinical use is realised using cut-offs such as (a) <10th, 5th or 3rd centile to identify babies with degrees of growth restriction and (b) >90th centile to identify babies that have been potentially exposed to gestational diabetes and/or are at risk due to macrosomia.

2.3 Fetal-weight growth models

2.3.1 Definition and derivation

Fetal-weight (FW) standards are derived from the values of measured ultrasound biometry introduced in the 1980s and 1990s and, given the effect of pathology has been excluded, are an estimate of the way a normally developing fetus should grow independently of factors that might trigger the birth process. Individual biometric standards are derived from ultrasonographic estimates of head circumference (HC), abdominal circumference (AC), femur length (FL) and biparietal diameter (BPD) [19] and although each of these can be used separately to reflect fetal growth, there is no neonatal equivalent for verification, whereas EFW, when calculated as a combination of one or more of these parameters [20], can be validated by the actual BW.

2.3.2 Cross-sectional studies

These are observational studies analysing data items from a population at separate gestations, often carried out when scanning resources are limited. Here, each pregnancy has one (or possibly more) scan measures used to estimate weight. Hadlock et al [3,20,21] in 1991 provided an early sonographic fetal weight standard through a single-measure, cross-sectional reference based on 392 pregnancies and this has been widely used since. Later, in 1996, a national Swedish multi-measure standard based on 759 scans from 86 pregnancies was published by Marsal et al [22].

2.3.3 Longitudinal studies

Here, each pregnancy utilises a number of scans at different gestations for each pregnancy enabling selected growth models to be fitted and tested and the most suitable applied. An early population reference was presented by Gallivan [23] in 1993 (London, UK) producing tables for AC and EFW, and five years later the selective, high-risk Amsterdam cohort of de Jong [24] tested the way physiological variables affect fetal weight gain in a pathological population. More recently, a prescriptive EFW standard has been produced in the USA by Buck Louis et al [25] (National Institute of Child Health and Human Development, 12 US sites) and internationally by Stirnemann et al [26] (IG-21, 8 urban areas) and Kiserud et al [19] (World Health Organisation, WHO, 10 countries).

2.4 Discussion and critique

It is not uncommon for the authors of population weight references and standards to acknowledge the limitations in their models. One of the most common is 'factors other than gestation and sex directly affect weight' [16] [27]. Another is 'growth and weight difference due to altitude' documented by Lubchenko et al [18] who acknowledged that their early high-altitude Colorado birthweight standard would not necessarily be descriptive of other populations and Krampl et al [28] argued against uniform population-based charts when comparing high (4300 m) and low (sea level) altitude's effects on fetal size in Peru. Goldenberg et al [29] (1989) and Kramer et al [30] (2001) both point out other factors that affect the assessment of birthweight including method of dating, hospital births vs population-based data and gestation approximated as rounded vs completed whole weeks.

A major consequence of differing standards is their effects on birthweight, in particular the P10 (10th percentile) and P90 (90th percentile) cut-offs that define babies as small and large respectively, and which are critical tools in clinical analyses. In an update to the Kramer [30] (2001) Canadian reference, Hajihosseini et al [31] highlighted ethnic birthweight variations in a large Alberta reference, documenting differences in SGA and LGA (large for gestational age) cut-offs by sex between South Asians, Chinese and the general population. Buck Louis et al [25] also reported "… significant differences in fetal growth among different racial/ethnic groups as exemplified by individual biometrics and EFW".

Figure 1 highlights similarities and differences in three significant fetal weight models. Here, we observe Hadlock and WHO (Kiserud [19]), two standards derived from different techniques and environments, sharing approximately the same fetal weight trajectory, whereas the two international prescriptive standards (WHO and IG-21) showed more than 250 g discrepancy, averaging a 6.5% weight difference over a 26-40 week range. The authors of the WHO standard reported that both FW and BW varied considerably between countries and suggested that the supplied growth charts "may need to be adjusted for local clinical use to increase their diagnostic and predictive performance" – which belies the 'one size fits all' (under optimal conditions) assumption of both WHO and IG-21. This was reinforced in an expert review by Grantz et al [32], comparing the NICHD, IG-21 and WHO standards, where they highlight the ethnic/racial/country differences in the three standards and relate these to the potential for misclassification of SGA and LGA. However, they comment critically on the current clinical use of size to represent growth and another Grantz et al [33] study, developed fetal growth

velocity (GV) standards. Here, they examined five biometric parameters, together with EFW, to complement size standards to show that GV adds additional information, but further research is needed to investigate links between GV centile and morbidity and mortality.

At preterm gestations, Gardosi [34], Hadlock and others [10 22 35] noted that the BWs of a significant proportion of infants fell below their respective EFW counterparts and Cooke [36] concurred that FW standards will thus identify otherwise hidden FGR. **Figure 2** shows this relationship pictorially with IG-21 birthweights presenting around 50g lower than their fetal counterparts up to 33 weeks gestation. The figure also displays the recent Nicolaides [37] London and Kent reference weight curve which displays around 500 g heavier than the two IG-21 standards from 30 weeks. They suggest that BW and EFW have a common median but less variation in EFW as preterm BW has an increased association with pathology, in particular fetal growth restriction. It is worth noting that although absolute IG-21 and WHO fetal weight standards differ, **Figure 3** shows that in relative terms there is little to differentiate between Hadlock, IG-21 and WHO when described through a proportionality model, as percentages of the respective 280-day fetal weights.

Chapter 3. The GROW customised model

> *"The farther a society progresses, the more clearly the individual becomes the antithesis of the group"*
>
> *Sir Herbert Read (1893-1968)*

3.1 Development and concepts

3.1.1 Origins and development

The customised growth centile and chart was developed initially in the UK Nottingham Perinatal Research, Audit and Monitoring Unit in the early 1990s [38] and broadened and improved in the later-formed Perinatal Institute in Birmingham from the late 1990s. Recognising the importance of growth for fetal well-being, it became increasingly clear that the general population charts commonly in use were unsatisfactory for a full clinical assessment in a heterogeneous maternity population. Over time, the concept of an adjustable or customised assessment of growth and birthweight became the GROW standard. The GROW knowledge-base, which allows application in different populations, is constantly being improved, added to and used in conjunction with the international data sent to the Institute for analysis and has now expanded to a database running at over 4 million anonymised births.

3.1.2 GROW customisation principles

The GROW standard is constructed based on data that excludes multiple births, premature deliveries (<37 weeks gestation), stillbirths and major congenital anomalies. The principles are:

3.1.2.1. Adjustment for individual variation. Weights are assessed to produce a standard at term, individually adjusted for physiological pregnancy variables and sex of baby.

3.1.2.2. Optimisation. The standard at term is 'optimised' to obtain the growth potential, by excluding the effects of pathological variables which yields a term optimal weight (TOW).

3.1.2.3. Application of a fetal weight standard. The techniques above are applied to a suitable term birthweight population and, when linked to a fetal-weight-based proportional growth formula or function (PGF), give an optimal weight or growth potential at any gestation – hence GROW (Gestation Related Optimal Weight)

3.2 Adjustment for individual variation and optimisation.

The GROW customised model is initially set up using non-pathological factors affecting birthweight: gestational age, maternal height and weight at booking, parity, ethnicity and sex of the baby [38] and categoric body mass index (BMI) variables are included within the model to estimate their effect but those outside the normal limits of 18.5-30 are excluded as pathological. Other pathological factors such as smoking**,** pre-eclampsia, hypertension**,** diabetes or social deprivation are also known to affect birth weight but, if they are available and included in the analysis, are also not adjusted for. Linking the PGF to the calculated TOW value generates an ideal or optimised standard against which actual fetal or neonatal weight can be assessed and will more easily recognise if growth and weight has been affected by pathological factors.

Model coefficients are derived from suitably large birth databases using a multiple regression (MR) model based on sound principles [1] and centred on a baseline or 'standard' mother for comparison purposes, of height 163 cm and weight 64 kg at booking (first visit), of European ethnic origin in her first pregnancy with 'average' (sex-neutral) baby gender delivering at 280 days. The regression covariate scale variables, gestation, maternal height and maternal weight, are transformed to deviations from their respective 'standard' values. The categoric variables sex, ethnicity and parity are coded according to their natural groupings but with reference to a standard default value: sex = female, ethnicity = most prominent, and parity = 0. The regression model produces a constant, representing the expected (P50) birthweight for the standard mother's baby, together with coefficients for each statistically significant independent variable. **Table 1** shows the original coefficients derived from a Nottingham database (1987-1991; n=38,114) [1] and are reproduced here for illustration only, as they have since been superseded.

MR coefficients are used to calculate individual deviations (add-ons) for each baby which are added to the constant to produce their individual TOW as follows:

$$\text{TOW} = \text{constant} + \text{htao} + \text{wtao} + \text{ethao} + \text{parao} + \text{sexao} \qquad [1]$$

where 'ao' is an add-on, respectively, for each of: ht = maternal height, wt = maternal weight, eth = ethnic origin, par = parity and sex = gender of fetus/neonate, if determined.

3.3 Application of a fetal weight standard

Once the TOW is calculated, a PGF is used to determine the percentage optimal fetal weight at any gestation. The PGF can be used:

- retrospectively, with birthweight to estimate previous fetal weight, or
- prospectively, using fetal weight to predict future birth weight [1] [39]

under the assumption that, throughout pregnancy, a) the influence of maternal and fetal characteristics is proportional, and b) relative variation is constant.

The PGF is derived from Hadlock's fetal weight equation [3], a log-polynomial of the 2nd order:

$$f_H(g) = \exp\,(0.578 + 0.332 \times g - 0.00354 \times g^2) \qquad [2]$$

where: exp is the exponential (Euler's) function,
g is gestation in exact weeks, between 10.0 and 40.0, and
$f_H(40.0)$ = 3619.17, by substituting g=40.0 in [2].

By dividing [2] by the term weight 3619.17, we can express it as a PGF as follows:

$$\text{PGF}(g,\%) = \frac{f_H(g)}{3619.17} \times 100 \qquad [3]$$

This is known as the 'proportionality formula' and although it determines proportions precisely, an approximation was made in the originating paper [1] evaluating $f_H(g)$ at each gestation and subsequently refitting with an ordinary polynomial to give the following:

$$\text{PGF}(g,\%) = 299.1 - 31.85 \times g + 1.094 \times g^2 - 0.01055 \times g^3 \qquad [4]$$

where g is gestation in exact weeks, but only valid between 24.0 and 40.0.

3.4 GROW model limits of variability

We assume that birthweight is distributed approximately Normally and calculate the coefficient of variation (CV) for our target term data as:

$$\text{CV}\,(\%) = \frac{SD}{Mean} \times 100 \qquad [5]$$

where: SD is the standard deviation represented by the standard error of the regression, and
$Mean$ is the median or P50 value represented by the regression constant.

This statistic is used over all gestations to establish a range, normally between the 10th and 90th percentiles, outside which cases are considered non-optimal, and calculated as:

$$\text{Mean} \pm (z \times \text{CV})\% \qquad [6]$$

where: z is the value of a standard Normal distribution (or z-score) corresponding to specific limits
with: z = 1.28 for 10-90% limits (other values are obtained from published tables [40])

Using the **Table 1** example, SD = 389 g, mean = 3478 g which gives CV ≈ 11% using [5] and we have 10-90 % limits as:

$3478 \pm 1.28 \times 11\%$ = $3478 \pm 14\%$
= 2991 – 3964 g.

3.5 Customised centiles and growth charts

Both customised centiles and growth charts are generated with reference to a data standard (for example the original Nottingham standard of **Table 1**) containing a regressed constant with coefficients for significant variables, and then individualised to obtain a TOW as in [1].

A **customised centile** can be calculated by:

a) proportionalising the TOW to the relevant gestation using the PGF in [3] or [4] to obtain expected weight (*ewt*),

b) calculating a z-score as the standardised deviation of the observed weight (*owt*) from the *ewt* as follows:

$$z = \frac{owt - ewt}{0.11 \times ewt}$$

c) converting to a (per)centile using standard normal tables [40].

A **customised GROW chart** with 10-90 percentile lines is produced by:

a) generating a TOW as in [1], but *without a sex add-on* since it is an antenatal chart,

b) proportionalising TOW over the gestational range as in [3] or [4] to obtain a curve of EFWs

c) using the previous variability limits as in [6] with mean = EFW, CV = 0.11 and z = 1.28 to give:

$$\text{EFW} \pm (0.11 \times 1.28 \times 100\%) = \text{EFW} \pm 14\%,$$

which defines the P10 and P90 lines as ± 14% below/above the EFW curve, respectively.

Individual GROW charts improve the detection of fetal growth problems antenatally, avoiding unnecessary investigations and thus reducing anxiety by reassuring mothers when growth is normal. The chart is used to plot fundal heights and/or scan weights periodically and a representation of such a chart is shown in **Figure 4** where, in the example shown, a slowdown in growth is being clearly indicated by the last three scan plots.

3.6 Other models associated with the GROW technique

3.6.1 The Dutch Generation R study [41] formed the basis for Gaillard et al [42] to present the first fetal-weight-based customised model using physiological maternal and fetal characteristics, and provided an EFW formula. They also suggested (with evidence at 20 and 30 weeks) the effects of some maternal and fetal factors are not necessarily proportional but concluded that further studies were needed to validate their technique.

3.6.2 Tarca et al [43] published a customised fetal growth standard for African American women (PRB/NICHD) and compared it with three others, including GROW, identifying a larger percentage SGA. They found that: a) the effects of maternal weight and parity differ with gestation and those of maternal height and parity with fetal size, and b) agreement among standards was related to number of common covariate factors.

3.6.3 Where regions or countries do not have data on the factors necessary to derive individually adjustable coefficients, a simplified version of GROW, known as GRAW (Gestational Related Average

Weight), can be used to generate a population average growth chart. The GRAW application has been available from the Perinatal Institute and has already been supplied for use in some countries where full customisation was not possible or desired. Mikolajczyk et al [44] created a similar 'generic reference' applying and validating the technique using the WHO Global Survey data from 24 low- and middle-income countries.

Chapter 4. The GROW customisation rationale

I have described how the GROW individual customised standard was devised as a progression from a 'one size fits all' population reference or standard which does not integrate factors known to affect fetal weight and birthweight and this is supported in the short paper by Resnik [45]. Using our tools, international teams have constructed customised standards for clinical use from, for example, datasets in Australia [46], New Zealand [47], Spain [48] and Ireland [49].

4.1 Generic benefits of the GROW standard

4.1.1 Accounting for population heterogeneity and application to subgroups

The customised standard produces centiles and charts that are adjusted for individual pregnancy characteristics known to influence weight [1] and consequently more able to represent an individual within a diverse population. It will thus be sensitive to differences between clinically significant subgroups [50], for instance: low vs mid vs high BMI; primiparous vs multiparous; European vs South Asian ethnicity.

4.1.2 Accounting for prematurity

Because of the link between prematurity and IUGR (intra-uterine growth restriction), the customised model, in defining growth potential, does not rely on preterm birthweight distributions which by definition are derived from pregnancies with a pathological outcome. Instead, it uses a fetal weight proportionality formula [1] derived from Hadlock's ultrasound-based fetal weight standard [3] to adjust for gestational age. The proportionality curve based on Hadlock has been shown to be similar [51] when based on the IG-21 [26] and WHO [19] standards in describing the growth trajectory in utero.

4.1.3 Improved clinical confidence.

Due to the construction of an optimal standard statistically related to the individual mother's physiology, a small mother could produce a constitutionally small but normal baby displaying AGA, with 10 < customised centile < 90 confirming that the baby is not at a higher risk of adverse outcome [50]. However, using a population standard, many newborns displaying within a normal range but showing adverse characteristics of FGR neonates, such as malnutrition or metabolic and haematologic disorders, are picked up through customisation [45]. The reduced misclassification through the use of customised charts improves clinical confidence.

4.2 Critiques of GROW and responses

Published critical examinations of GROW are few, but five are presented in the sections below where they:

1. challenge one or more aspects of the GROW principles,
2. question the relevance of particular contributing variables,
3. use non-standard techniques or factors, or
4. construct GROW models in an analytically incorrect manner.

Their assertions are stated and then deconstructed, generally through published responses, which aim to impugn their arguments.

4.2.1 Zhang et al [52] asserted that the increase in perinatal mortality risk within SGA found using customisation is artefactual due to the inclusion of more preterm births and mothers with high BMI.

In reply [53], it was pointed out that SGA linked to prematurity is de facto better detected because GROW uses a fetal weight standard which avoids limits based on preterm birthweights that are skewed due to their known association with fetal growth restriction. An explanation for this improved discrimination may be that the more severe the condition underlying the growth deficit, the earlier the fetal demise. However, the improved link with stillbirth risk using a customised standard, while being particularly clear in the preterm period, nevertheless also holds at term. As regards obese mothers, customisation identifies a large hidden subset of SGA babies that are at a higher stillbirth risk [54].

4.2.2 Hutcheon et al [55] argued that the main benefit of customisation was the application of the Hadlock fetal weight curve and questioned whether adjusting for maternal characteristics mattered.

We found that their comparative analysis, comparing a GROW with a Hadlock population model to find similar relative risk (RR) values for mortality, was flawed. Their construction of a customised model was incorrect on two major counts. First, they transformed maternal weight from a naturally continuous variable to discrete categories, which automatically blunts its effect. Second, they did not identify and exclude pathology which dampens the ability of the centiles to optimise the model and thus reflect its full growth potential. I correctly applied a customised standard in Publication 2 [56] (see following chapter) to refute their claims which demonstrated that, when the fetal weight element is equalised by applying it to both standards, customisation, with its inclusion of maternal characteristics, substantially strengthens association with perinatal mortality risk.

4.2.3 Carberry et al [57] found their own derived customised standard showed no advantage over a local population standard when predicting growth and perinatal morbidity from term birthweights in Sydney, Australia.

Gardosi et al [51] found this to be an interesting study because it assessed outcome through perinatal morbidity indices and neonatal body fat with the use of air displacement plethysmography, the latter being atypical. Together with the fact that the customisation parameters were based mainly on maternal recall, we felt the results of their comparison were weak.

4.2.4 Iliodromiti et al [58], in a large term database in Scotland, compared a partial customisation model using only maternal height and parity with a non-specified population standard and found that the association of SGA with stillbirth and infant death was not improved.

It is not surprising that partial customisation, particularly without two of the most significant concomitant variables affecting birthweight – maternal weight and ethnicity – was not efficacious. Given that there was considerable missing maternal height data and the statistically questionable [59] Net Reclassification Index was used in the analysis, I feel this challenge is superficial.

4.2.5 Ego et al [60] questioned whether parity was worth adjusting for in a customised standard since they found that their comparison of customised models with and without adjustment for parity showed no difference in the identification of high-risk babies and perinatal mortality.

In reply [61] we presented two arguments. First, we noted that Ego showed that non-adjustment for parity increased the nulliparous SGA rate from 14.9 to 18.0% and considered this a favourable effect showing a higher risk. Our first point is that if customising without parity does not improve association with adverse outcome, then a lower SGA rate would avoid extra investigations and we simply note that the management of the complications of nulliparous risk should not depend on increased SGA numbers. Second, using a Swedish database [54], we tabulated, for each parity group, mortality and SGA rates, the latter with parity (model 1) and without parity (model 2). **Table 2** reproduces these results and shows a U-shaped relationship between mortality rates and parity with the highest in the Para 4+ category. Model 1 mirrors this pattern whereas model 2, without parity adjusted for, has a greatly increased SGA rate in the nulliparous category to a degree not reflected in the mortality rate. The relationship between perinatal mortality and SGA rate is stronger for model 1 (r=0.94) compared to model 2 (r=0.24), although the difference is not statistically significant due to the small number of parity category comparisons.

Chapter 5. Case studies: a selection of published papers

The following eight selected published papers, and the body of work they represent, developed and tested the method of customising birthweight centiles and their use in the construction of individual growth charts. The main underlying hypothesis throughout was that adjusting the standard of assessment for maternal and pregnancy characteristics improves the identification of pathology and assists clinicians by being better able to target their investigations and interventions to help prevent adverse outcome. Within all the papers, my role was to help investigate, analytically and statistically, the validity of our method and its application to answer clinical questions and challenges for improving perinatal care.

5.1 Validation of GROW against other standards and outcomes

The first three publications used a range of techniques to validate the GROW customisation method, by comparison with various population-based techniques, to see how well each identifies morbidity and mortality through their respective determinations of SGA.

5.1.1 Publication 1 [62] Link

Jason Gardosi, Andre Francis;

Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles;

Am J Obstet Gynecol. 2009;201(1):28.e1-28.e8.

5.1.1.1 Objective

The purpose of the study was to investigate and compare the association between SGA, derived from population (pop) and customised (cust) limits, and several indices of pregnancy complications and adverse outcome.

5.1.1.2 My contribution

I used data from a USA NIH multicentre study [63] to derive a pop standard to allow fair comparisons with the previously published cust standard [64] based on the same data. Non-normality of weekly birthweights required use of the LMS method [65] to generate and smooth 10th, 50th and 90th centile birthweight curves. I then constructed intersecting Venn Diagrams to show the interaction between SGA identification by pop and cust categories, highlighting three subcategories, pop-only, cust-only and both to demonstrate how cust-only identified twice as many additionally recognised cases than pop-only. In order to better identify adverse outcomes that are associated with SGA at preterm gestations (e.g. preeclampsia), birthweights for cust-only and pop-only were then plotted against 10, 50 and 90th centile lines by the population standard to compare the association between growth failure and spontaneous preterm delivery, showing the distribution of the one-quarter of cust-only SGA that were born preterm. The same five groups were then compared through odds ratio (OR) risk analysis and displayed on log-scale graphs for each of the six SGA-associated adverse outcomes.

5.1.1.3 Findings

The collective analyses convincingly demonstrated that over all the adverse outcomes, SGA defined by a customised standard gave a consistently (and significantly) higher risk than SGA by population methods, with 3 of the 6 in the latter not reaching significance.

5.1.1.4 Impact (45 citations)

Many studies have reached similar conclusions from diverse international populations. Examples are de Jong [66] (Netherlands 1998), McCowan [67] (New Zealand 2005), Ego [68] (France 2006), Odibo [69] (USA 2011) and Moon [70] (South Korea 2016), all of which compared a customised local standard with a commonly used population standard.

There are currently over 500 registered UK and international researchers able to generate GROW customised centiles through our calculator tools (https://www.gestation.net/cc/about.htm).

5.1.2 Publication 2 [56] Link

Gardosi J, Clausson B, Francis A;

The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size: Value of customising centiles for parity and maternal size;

Br J Obstet Gynaecol. 2009 Sep;116(10):1356–63.

5.1.2.1 Objective

This study investigated the way customised and population definitions of SGA fared in their assessment of how perinatal risk is associated with clinical categories of parity and maternal size. It was motivated by claims [55] that the benefit of customisation lies solely in the use of the fetal-weight-based proportionality model [1]. I used the same proportionality model, one with customisation and the other without, based on the average of the same population and our aim was to examine how SGA defined by one or the other method correlated with perinatal mortality risk.

5.1.2.2 My contribution

My statistical role involved preparing and checking variables, deriving a maternal size variable with categories based on weight with corresponding increasing maternal height so as to stay within normal BMI limits. I analysed (a) the association between mortality and SGA in the four categories in each subgroup for the two models, using slope comparisons via t-tests; and (b) how the two models' SGA risk compared within subgroups through risk analysis with RR.

5.1.2.3 Findings

The results demonstrate that adjusting for parity and maternal size results in derived SGA which substantially strengthens association with perinatal mortality risk. The argument that once gender and fetal-weight growth have been accounted for, further adjustment for maternal characteristics added no benefit, is not supported by this analysis.

5.1.2.4 Impact (112 citations)

The clinical implications of our findings are that mothers present clinically with different characteristics, including height and weight, which have a constitutional effect on the optimal size of the baby; adjustment for such variation can give the clinician increased confidence when assessing fetal growth against a standard that is adjusted for such variation. For example, small but normal babies could be classified SGA (rather than AGA) if maternal size is not considered, causing unnecessary intervention and worry.

5.1.3 Publication 3 [71] Link

Francis A, Hugh O, Gardosi J;

Customized vs INTERGROWTH-21st standards for the assessment of birthweight and stillbirth

risk at term

AJOG. 2018;218(2):S692-699.

5.1.3.1 Objective

Using databases from Bhutan, China, Germany, India, Ireland, Netherlands, Slovenia, Sweden, UK and USA, the main intention of this paper was to compare two competing birthweight standards, IG21 [5] and GROW with conceptually opposite foundations, to assess how well they were able to associate birthweight with stillbirth risk when applied to an international cohort.

5.1.3.2 My contribution

As the senior statistician of the Perinatal Institute, I was responsible for the management of datasets sent to us for analysis from many countries, which formed our anonymised international database. For this study, I compiled a cohort of the 10 sets which recorded stillbirth as a pregnancy outcome, restricting cases to term deliveries and the main ethnic group in each country. Our global centile calculator was used to produce customised centiles, and IG-21 centiles were computed according to their published standard [5]. The 10 cohort characteristics were tabulated, including SGA and LGA rates based on each method, which demonstrated just how different the two standards are. I set up a 'predicted weight' comparator based on the term optimal weight (TOW), adjusted for each country's maternal characteristics and then controlled for gestation at delivery. I then separately compared predicted weight with (a) unadjusted birthweight, (b) IG-21 SGA rate and (c) IG-21 LGA rate using scatter plots with fitted regression curves to demonstrate their high correlation. Risk analysis was used for comparing how GROW and IG-21 differed in their detection of both SGA and LGA cases that the other missed using a 5-group tabulation: GROW only, all GROW, both GROW and IG-21, all IG-21 and IG-21 only, using SB, RR and PAR (population-attributable risk) statistics.

5.1.3.3 Findings

This study demonstrated the ability of GROW customised assessment to identify a significantly large number of stillbirths that the population-based IG21 technique misses in this international cohort. We argue that IG21's wide variation in both SGA and LGA rates are only reflecting differences in physiological / maternal constitutional characteristics in the various countries.

5.1.3.4 Impact (57 citations)

The study is consistent with others that independently compared GROW with INTERGROWTH-21st, using a variety of pregnancy outcomes, such as Pritchard et al [72] (Australia), Fay et al [73] (USA), Savirón-Cornudella et al [74] (Spain) and Anderson et al [75] (New Zealand).

5.2 Application of GROW principles to understand causes and improve prevention of adverse events

These five studies demonstrate how the GROW customisation technique has been applied to form the basis of some clinically significant findings**.**

5.2.1 Publication 4 [76] Link

C.L.D. De Jong, A. Francis, H.P. Van Geijn and J. Gardosi**;**

Customized fetal weight limits for antenatal detection of fetal growth restriction;

Ultrasound Obstet Gynecol. 2000;15(1):36–40.

5.2.1.1 Objective

To determine cut-off limits for customised fetal weight standards in identifying fetal growth restriction and related perinatal outcomes in a population at increased risk of uteroplacental insufficiency.

5.2.1.2 My contribution

From 1197 3rd-trimester scans, based on 215 valid pregnancies, I used those where the lag between last scan and delivery was < 7 days to compare methods of fetal weight estimation, and selected Hadlock (AC, FL) or Campbell (AC), if FL was missing, which had the smallest systematic error for this data. Each of the four outputs: operative delivery for fetal distress, low pH, NICU admission and customised birthweight SGA, gave sufficient numbers to generate a performance characteristics table (sensitivity, specificity, PPV and NPV) using an FGR diagnostic test defined as 'number of cases with at least one EFW < 10th customised percentile'. ROC curves were constructed, varying the customised centile to determine optimal cut-offs for each outcome, which were then used to rerun the performance characteristics table.

5.2.1.3 Findings

It was shown that FGR was diagnosed over two-thirds of the time using 'at least one EFW < cust P10' and that 18% (in practice 20%) was an optimal cut-off for SGA in this high-risk population, giving an improved detection rate of 83% compared with 68% at the usual 10% cut-off. The two significant FGR-associated perinatal complications, fetal distress and NICU, had optimal cut-offs of 8% suggesting that a 10% cut-off was practical for identifying them.

5.2.1.4 Impact (322 citations)

Three other studies utilised this data.

- De Jong et al [66] showed that customisation identified more cases at increased risk for adverse perinatal events than the local Netherlands standard.
- Another study [24] used longitudinally-derived, log polynomial growth curves to compare patterns of growth in subgroups of maternal height and weight, parity and sex. Height and weight differed in subgroup value for fetal weight but not in growth per day over the last two weeks whereas the opposite was true for parity and sex.
- De Jong et al [77] compared the same adverse outcome measures as this publication to show that they had slower average growth rate (grams / day) over the six week period prior to birth, suggesting growth restriction.

5.2.2 Publication 5 [78] Link

Jason Gardosi, Sue M Kady, Pat McGeown, Andre Francis, Ann Tonks;

Classification of stillbirth by relevant condition at death (ReCoDe): population-based cohort study;

BMJ. 2005;331(7525):1113–7.

5.2.2.1 Objective

We wanted to introduce a new classification system for stillbirths, involving the use of GROW customised centiles to identify growth restriction as a specific condition present at death. Up to this time, the majority of stillbirths were classified as 'unexplained' and our approach was, first, to direct attention from attempting to determine 'cause of death' to identifying 'condition(s) present at death' (ReCoDe – relevant condition at death) and second, to investigate what contribution fetal growth restriction made as a relevant condition preceding stillbirth.

5.2.2.2. My contribution.

As the statistician and senior analyst my responsibilities were to (a) oversee the cleaning, verification, validation and compatibility of data between disparate IT systems, (b) to identify those cases that were growth-restricted, defined as SGA <10th customised centile, and (c) write code (on an Excel platform) to convert the previously-used Wigglesworth categories, in conjunction with clinically-led coded ICD-10 classifications, to the new ReCoDe groups and subgroups. Using these, I applied a two-stage hierarchical table displaying primary and secondary classifications with derived statistics.

5.2.2.3 Findings

We found that the use of customisation in the identification of FGR enables the identification of 'fetal growth restriction' as a condition in ReCoDe often underlying stillbirth and, taken together with an extended hierarchical classification, explains most of the traditional Wigglesworth 'unexplained'. This link has implications for preventative health policies since, through enhanced efforts to increase antenatal detection of FGR, more stillbirths will be prevented.

5.2.2.4 Impact (308 citations)

- ReCoDe showed the smallest proportion of unexplained stillbirths when Vergani et al [79] compared it with a number of traditional and new classification systems.
- In a 7-country international comparison of 6 classification systems [80], ReCoDe was acknowledged as performing well when measuring such qualitative factors as information retainment, ease of application and 'operator reliability' as well as the proportion of unexplained cases.
- ReCoDe continues to be used in perinatal mortality audits both in the UK and internationally.
    - In Sheffield (2019), Blythe et al [81] used the technique to investigate 'clinically unexplained stillbirths' to find that over 60% were diagnosed at post-mortem to have FGR and/or placental insufficiency.
    - Gaia Po et al [82] (2019) in Emilia-Romagna region, Italy, evaluated the implementation of a regional audit system for stillbirth. ReCoDe was chosen over a number of classification systems for "retaining important information and ease of use" as well as a low proportion of unexplained cases (14%).

    - Ying Hu et al [83] (June 2021) in Zhejiang Province, Southern China published a targeted case-control investigation of third trimester stillbirths using ReCoDe which yielded under 9% unexplained.
- ReCoDe was further used in my analysis and transformation of a joint West Midlands and South African dataset forming part of our collaboration with WHO [84,85]. This involved the first application of the new ICD-PM perinatal mortality classification system which transformed a singular baby death classification system into a mother-baby dyad structure, subsuming ReCoDe.

5.2.3 Publication 6 [86] Link

B Jacobsson, K Ahlin, A Francis, G Hagberg, H Hagberg, J Gardosi;
Cerebral palsy and restricted growth status at birth: population-based, case-control study;
BJOG Int J Obstet Gynaecol. 2008;115(10):1250–5.

5.2.3.1 Objective

We investigated whether there was an association between FGR defined by customised weight centiles and the subsequent development of cerebral palsy. Many previous studies had used low birthweight as a proxy for FGR. This study was able to utilise the high quality Hagberg database of cerebral palsy (CP) from Sweden.

5.2.3.2 My contribution

I verified that the matching physiological and gestational age comparisons were compatible for this case-control study using appropriate tests and specifically constructed the comparative groups of preterm and term age categories by customised centile category. These were then compared using OR risk analysis techniques.

5.2.3.3 Findings

Term births showed substantial association between fetal growth restriction and the subsequent development of cerebral palsy, the strength of which is linked to the severity of the restricted growth status. However, preterm births showed no association, suggesting a different mechanism responsible for the increased cerebral palsy risk.

5.2.3.4 Impact (129 citations)

The results, particularly the correlation between severity of FGR and likelihood of CP, contribute to the evidence base suggesting that CP has a predominantly antenatal, rather than a labour-related, cause.

- Dahlseng et al [87] (2013) reinforced our results by studying length, HC and other parameters, as well as birthweight, of term-born singletons to show most subtypes of CP have displayed poor intrauterine growth due to antenatal factors.
- McIntyre et al [88] also studied antecedents of cerebral palsy and found that “Fetal growth restriction ……recognized by age 6 years was a more substantial contributor to cerebral palsy and neonatal death than potentially asphyxial birth events and inflammation”.

5.2.4 Publication 7 [89] Link

Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A**;**

Maternal and fetal risk factors for stillbirth: population-based study;

BMJ [Internet]. 2013;346(3). Available from: https://doi.org/10.1136/bmj.f108

5.2.4.1 Objective

We explored the role of empirically proven risk factors for stillbirth throughout pregnancy and estimated their level of contribution.

5.2.4.2 My contribution

I led the epidemiologist and data investigation team in the exploratory analysis and identification of independent single and multiple explanatory variables, including two-factor interactions, on stillbirths through various regression models. The dependent variables used were those with a history of clinical relevance over a range of demographic, medical and social factors. We decided on Poisson regression techniques to model relationships and due to stillbirth rarity, standard errors were calculated through a bootstrap resampling technique and adjusted RR and PAR were used as the main comparative statistics. A sensitivity analysis was conducted to ensure excluded factors, repeat pregnancies and maternity unit clustering did not contribute to results bias.

5.2.4.3 Findings

It was clear that, although there were risk factors for stillbirth evident in early pregnancy, the most significant overall factor was FGR, as defined by customised birthweight centiles. FGR and smoking were the only two factors to show significant interaction, underlining the need for early pregnancy smoking cessation. It is clear that increasing antenatal detection of FGR reduces the risk of stillbirth.

5.2.4.4 Impact (368 citations)

According to the British Medical Journal website (https://www.bmj.com/content/346/bmj.f108/article-info), the full paper has been viewed over 53,000 times and downloaded over 10,000 times. Apart from the association between risk factors and stillbirth, the study is often also quoted in its ability to demonstrate that antenatal recognition of SGA reduces stillbirth risk. This underpins the rationale for antenatal surveillance strategies aimed at detection of FGR, as shown in publication 8.

5.2.5 Publication 8 [90] Link

Gardosi J, Giddings S, Clifford S, Wood L, Francis A;

Association between reduced stillbirth rates in England and regional uptake of accredited training in customised fetal growth assessment;

BMJ Open. 2013;3(12):e003942.

5.2.5.1 Objective

We analysed national and regional stillbirth trends to examine their association with accreditation training in fetal growth surveillance and evidence-based protocols.

5.2.5.2 My contribution

My role involved data and statistical analysis and advice, with access to, calculations for and assimilation of data from Office of National Statistics (ONS) data sources. This involved both live and stillbirth data (from 24 weeks gestation) using mortality statistics releases from 2007 to 2012. In order to smooth short-term fluctuations and highlight longer-term trends, rates for stillbirths were presented as 3-year moving averages superimposed on individual years. I advised on the construction of charts and tables, and the correlation measures and chi-squared tests for trend.

5.2.5.3 Findings

Stillbirth rates had dropped significantly in regions with a high uptake of accreditation training in fetal growth surveillance and evidence-based protocols, whereas low uptake regions saw no change in stillbirth rates. A Bradford Hill analysis [91,92] showed that, while this was an observational study only, the observed association was causal.

5.2.5.4 Impact (53 citations)

These results helped Trusts and Health Boards in their choice of whether to implement the Perinatal Institute's GAP (Growth Assessment Protocol) programme including customised charts. Associated studies included the following.

- An NHSE-funded project SaBiNE [93] (Saving Babies in North England) to assist with the implementation of GAP in three Northern National Health Service (NHS) regions, 2014/15.
- The SPIRE study [94] by Manchester University, assessing the implementation of the NHS England's Saving Babies' Lives care bundle which included FGR surveillance, confirmed that the reduction in stillbirth rates in participating GAP sites exceeded that reported nationally.
- More recently, a dose-dependent association between SGA detection and stillbirth prevention was confirmed in a 10 year study of ONS data [92].
- New Zealand [95] and Australian [96] observational studies confirm the improved detection of SGA using customised charts and the GAP program.

Chapter 6. Discussions and Appraisal

My two quotes, at the beginning of chapters 2 and 3 respectively, are intended to metaphorically differentiate between the population-based and GROW approaches to growth modelling; the former stamps the individual with a group identity, the latter personalises each member of the group with an individual identity.

6.1 GROW customisation

I have specified the principles upon which GROW is based, the technical aspects of its construction and how it can be considered as a tool for assessing both fetal weight and birthweight by uniquely combining a proportional fetal weight growth rule with a physiologically-adjusted and optimised

birthweight standard at term. It seamlessly incorporates the effects of the significant factors that have been shown to affect normal baby weight.

These principles underlie the main strength of GROW, which is the ability to account for individual variation and address the needs of subgroups of the population. As a result, more cases are identified with adverse outcomes than is accomplished using population based methods.

The GROW model assumes that the variables shown to significantly affect birthweight at term also apply at earlier gestational ages, through the backward projection of the predicted term optimal weight, using the proportionality curve. This is supported by evidence that similar variation associated with maternal characteristics such as height, weight and parity have also been observed in longitudinal ultrasound studies in low [97] and high risk [24] populations. Furthermore, the concept of 'proportionality' has been shown to be independent of the fetal growth chart used, applying similarly to WHO [19] and Intergrowth 21st [98] as they do to Hadlock [3] (See also Figure 2 in [51]; reproduced in Figure 3, page 43).

6.2 Population-based techniques

I have described, through referenced and documented evidence in section 2.4, the limitations of traditional population-based growth references and standards. My particular argument with these techniques is their predilection to represent individual baby weight through a fixed group identity or 'one size fits all', based on an elementary platform of how weight is related to gestation, qualified where relevant by sex. Many authors nonetheless acknowledge that there are other factors affecting growth and weight such as ethnicity and other maternal characteristics not considered in a 'one size fits all' model. These are limitations that restrict the standard's ability to represent the weights of individuals and those belonging to subgroups of the population according to maternal size or parity. In the absence of adjustment for individual variation, I have shown that population-based standards such as IG21 perform badly compared to customised standards. And the WHO growth study, while also presented as 'one size fits all' standard, reports clear physiological variation between cohorts in their multinational dataset [19].

The only advantage I can see for population-based standards is that they are simple to use, i.e. no maternal characteristics need to be collected and adjusted for.

6.3 Physiological and pathological considerations

The distinction between physiological and pathological aspects of factors affecting birthweight raises some interesting questions. Extremes of some natural physiological processes, such as maternal height, weight and parity, are associated with pathology. Zhang et al [99] demonstrated, using the Swedish Birth Registry and investigating short stature and primiparity, that both maternal height and parity showed pathological aspects and they conclude this has implications for customised birthweight standards. GROW already acknowledges this in taking maternal size into account by defining the maternal height-weight derivative BMI as pathological if it falls below 18.5 or above 25 and the variables so defined have almost always proved to be statistically significant.

Parity at either extreme is associated with increased risk. We have previously demonstrated increased risks for stillbirth of 80% for nullipara and 60% for para 3+ mothers [89] and there is also the well known association between nulliparity and pre-eclampsia [100] . However most parity-related variation in birthweight and fetal growth is observed in normal pregnancies. GROW, with a nulliparous 'standard mother' as its default, utilises parity in terms of its proven direct influence on birthweight showing parities of 1, 2 and '3 or more' significantly contributing to birthweight.

6.4 SGA definition

In a weight-for-gestation context, P10 has traditionally been the cut-off that defines SGA, with P5 and P3 as stricter refinements of the principle in order to include a greater proportion of pathological to physiological cases. Generally, the P10 cut-off is accepted and understood clinically and analytically but it is still accepted as relatively arbitrary.

Some publications have supported higher boundaries, for example, Xu et al [101] with a 15% cut-off based on variations in the risks of neonatal death and low 5-min Apgar. Also, we have shown, in a study of women considered to be at increased risk of uteroplacental insufficiency [76], an ROC optimal cut-off for fetal weight of 18%, implying that a rounded 20% limit might be more suitable for detecting the SGA baby antenatally, specifically in a high-risk population. However that study showed the 8th centile to be optimal for prediction of stillbirth, which could be rounded up to a 10th centile cut off in that population.

At the other end of the scale, Gordijn et al reported on the Delphi procedure [102] to determine an expert consensus definition of FGR which proposes, for late FGR, either a P3 cut-off or a combination of a P10 cut-off together with antenatal growth breaking a 25 percentile range (between two quartiles). They suggest that their proposals are intended to improve the definition of FGR since a P10 cut-off includes many constitutionally small fetuses that are at low risk for adverse perinatal outcome. However, the perceived advantages gained using the Delphi recommendation constraining a population-based FGR cut-off to 3% can be matched by using our normal 10% customised standard and this has been previously demonstrated through a large study using a Swedish national database [54]. Here, 2.5, 5 and 10% SGA cut-offs with numbers equalised were constructed in order to compare the two standards. **Table 3** reproduces statistics from this study showing that the stillbirth risk with SGA_{cust} at 10% (5.3) is similar to an interpolated SGA_{pop} at 3% and furthermore, the GROW PAR is nearly three times larger. Also, the fact that the PAR is 10 points higher for customised than population risk in comparable groups indicates that a larger proportion of pathology is present in the former and, since the groups have been constructed to have the same number of births, this pathology has been identified without an increase in the false positive rate. Therefore, the recommended cut-point relates to the intended use: the 10th centile captures more at risk cases (small for gestational age) while 5th or 3rd centile are more diagnostic and closer to 'fetal growth restriction'; but in each case, customising the limit according to constitutional factors improves the association with pregnancy outcome.

6.5 Conclusions and further considerations

Over the last 25 years, my analytical and statistical support has been at the heart of the contribution made by the Perinatal Institute's GROW customisation technique which has been integrated into the GAP programme and implemented through a variety of home- and web-based training and support programmes [103–105]. GROW has been endorsed by the Royal College of Obstetrics and Gynaecology [2] as the preferred clinical standard and recognised nationally and internationally through many prestigious awards [106].

The eight publications I have submitted illustrate the validation and application of the GROW customisation principles, highlighting for each: an objective, my contribution, key findings and impact. The first three publications consist of validation of the GROW standard compared with its population counterpart, and how the customised approach is more effective at identifying normal growth and growth-restricted pregnancy outcomes. The next five present various applications to which the standard has been applied to help understand how risk factors can help to identify fetal growth restriction, stillbirth, perinatal morbidity and cerebral palsy. A key finding in publication 7 was that improving antenatal recognition of fetal growth problems can reduce risk, helping to stimulate and focus health service initiatives on prevention. The final publication describes the results of the implementation of an early version of the GAP surveillance programme incorporating GROW charts across three English health service regions, leading to a significant reduction in stillbirth rates. This showed, using the Bradford Hill criterion [91], that even though the study was observational, the observed association was likely to be causal. Further causal association has been obtained in a larger study since, using 10 year data from the Office of National Statistics [92]. Comparing units which had full implementation of the GAP programme using customised GROW charts with others which did not, showed a significantly larger reduction on stillbirth rates, and a further increase in units with better antenatal detection of SGA.

The as yet unpublished DESIGN trial [107] was a cluster RCT which aimed to compare the effectiveness of the GAP programme with standard practice in antenatal detection of SGA. It is questionable whether it was able to achieve this aim reliably as, following training by the Perinatal Institute, delays in implementation resulted in too short data collection periods for the new programme to embed itself. Furthermore, the investigators defined SGA at birth as being small using <10th centile by *both* customised and population-based (UK90) standards, thereby disregarding the increased sensitivity of customised centiles to detect pregnancies at risk of adverse outcome. Such clinical studies are usually not powered to detect differences in the relatively rare 'hard' outccomes like stillbirth and neonatal death – instead, head to head comparisons to validate a chart need to come from epidemiological studies of large databases, as shown in several of the papers presented in this thesis. From all growth and birthweight standards in use today, GROW is the one that has been evaluated most extensively.

The next focus of work is to add growth rate or velocity as a parameter to the assessment of fetal size alone. Recent work has shown that the centile lines of customised GROW charts can also be used as normal limits of growth rate for sequential EFW measurements and are able to predict normal outcome, while growth trajectories that do not follow such limts are associated with adverse outcome [108]. There is also emerging evidence that assessment of growth velocity alongside size (EFW) can add significantly

to the identification of risk of adverse outcome [33,109] and such concepts will require prospective clinical evaluation.

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Table and Figures

Table 1: Original Nottingham study multiple regression coefficients

Model coefficients	Coeff	SE	p
Constant adjusted for 280 days	3478.4	389.0	
Gestational age (from 280 days)			
GA	20.7	0.482	<0.01
GA squared	-0.213	0.0384	<0.01
GA cubed	-0.00017	0.002937	0.95
Gender			
Male	58.4	4.18	<0.01
Female	-58.4	4.18	<0.01
Height cm (from 162.3 cm)			
Height linear	7.8	0.368	<0.01
Weight kg (from 64.3 kg)			
Weight linear	8.7	0.24	<0.01
Weight quadratic	-0.117	0.0140	<0.01
Weight cubic	0.00072	0.000240	<0.01
Ethnic group			
Indian subcontinent	-186.0	16.30	<0.01
Afro-Caribbean	-127.5	18.31	<0.01
Other	-65.1	25.56	
Parity (reference 0)			
1	108.0	12.74	<0.01
2	148.6	13.51	<0.01
3	149.9	15.86	<0.01
4 or more	149.8	18.62	<0.01
Smoking (number of cigarettes/day			
1-9	-152.5	13.60	
10-19	-214.5	14.77	<0.01
20+	-246.0	14.72	<0.01

Table 2: Perinatal mortality and SGA in customised models with and without parity using national Swedish births 1992-1995

Parity (after birth)	**Perinatal mortality** (per 1000)	**Model 1 SGA customised with parity** (%)	**Model 2 SGA customised without parity** (%)
1	5.6	12.7	17.2
2	4.2	11.6	10.0
3	5.3	12.3	9.4
4+	6.2	14.0	10.6

Table 3: Comparing population and customised standards through stillbirth rates and risk using national Swedish births 1992-1995

		Stillbirths			
	N	n	Rate/1000	OR *	PAR (%)
SGA_{pop} (%)					
2.5	8,017	117	14.6	6.0	10.7
5	14,163	159	11.2	4.7	13.8
10	30,815	238	7.7	3.4	18.5
SGA_{cust} (%)					
2.5	8,018	196	24.4	11.2	19.6
5	14,186	246	17.3	8.3	23.8
10	30,818	323	10.5	5.3	28.9

* Reference group is non-SGA births by both standards

Figure 1: Comparing the distributions of Hadlock, WHO and IG-21 fetal weight models

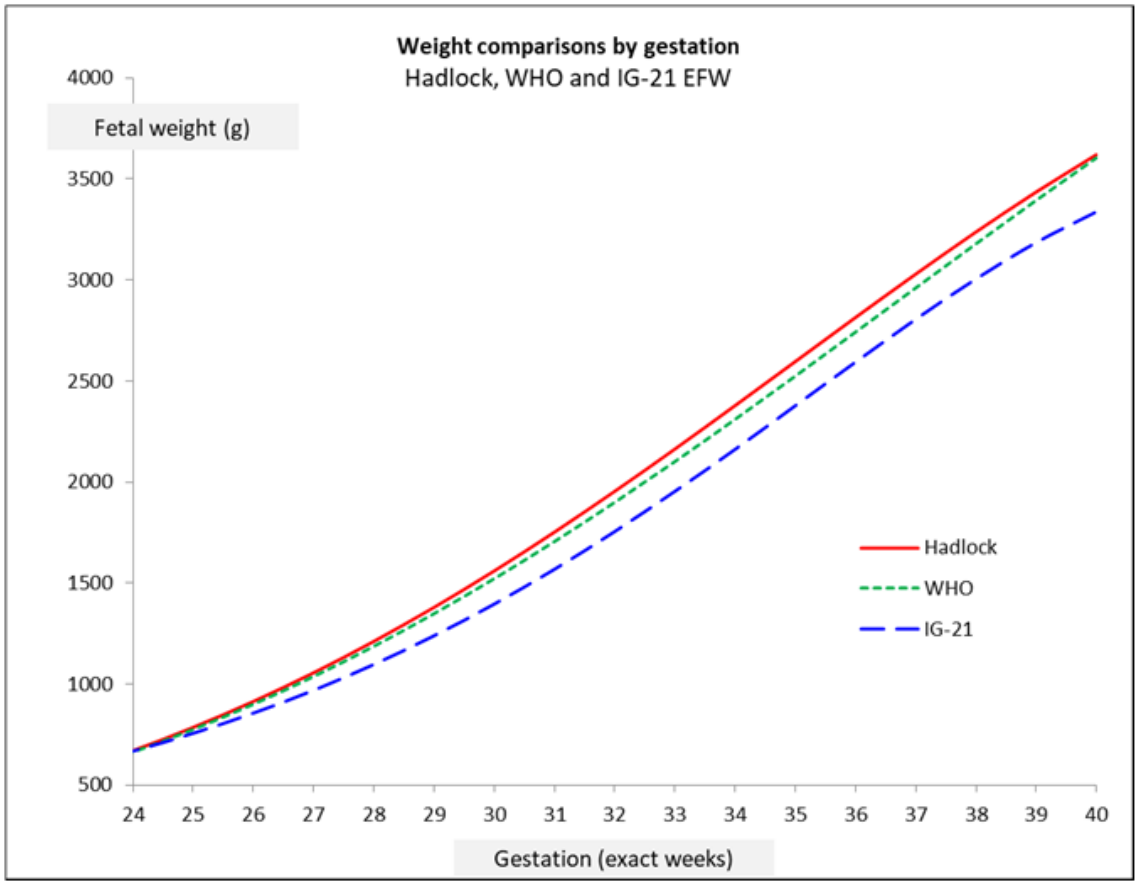


Figure 2: Contrasting IG-21 fetal and birthweight models with the Nicolaides model

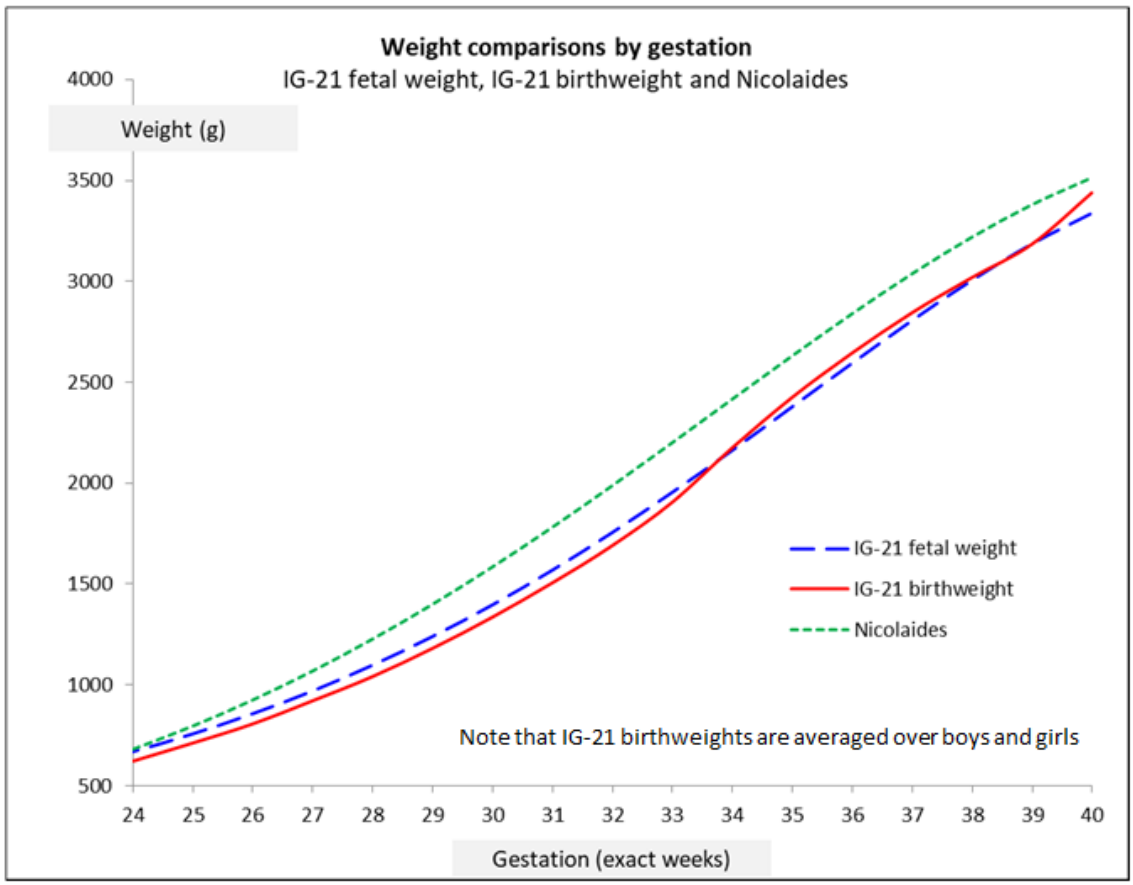


Figure 3 Comparing Hadlock, IG-21 and WHO fetal weight proportionality models

(see Fig 2 in [51])

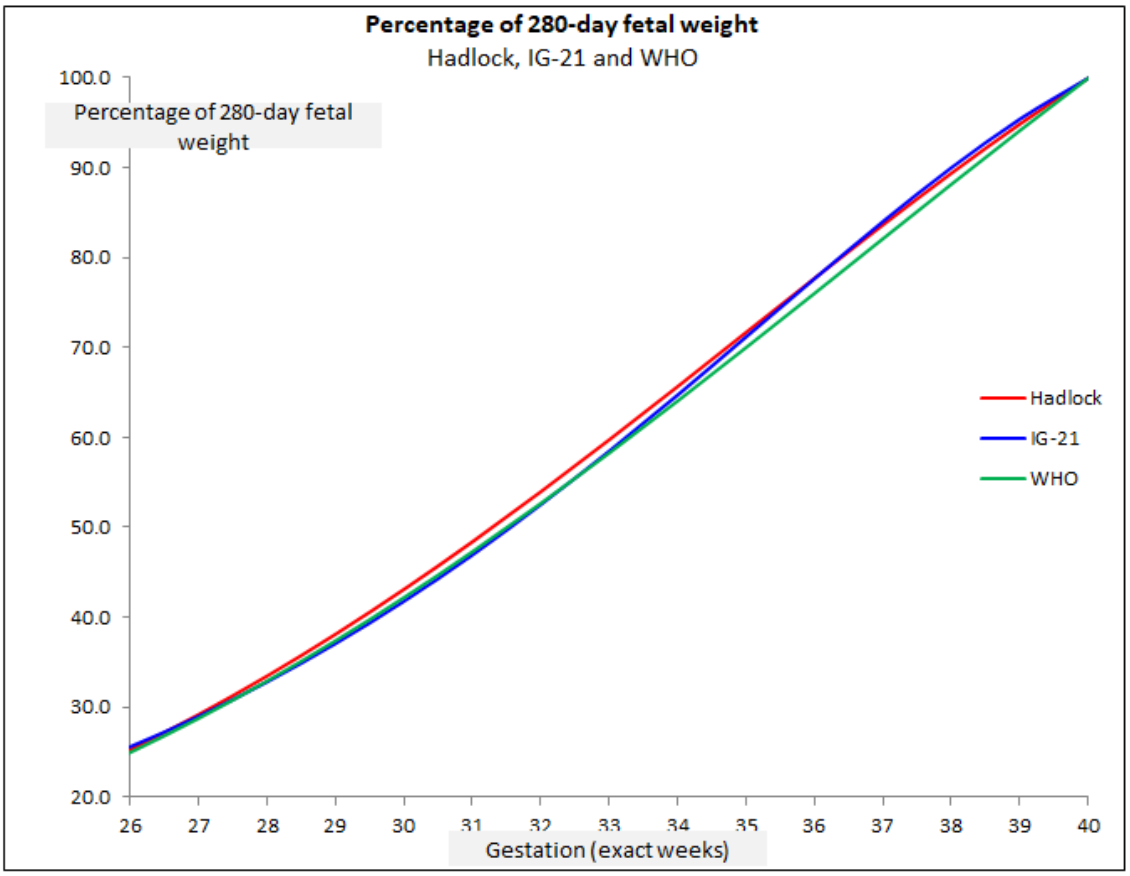
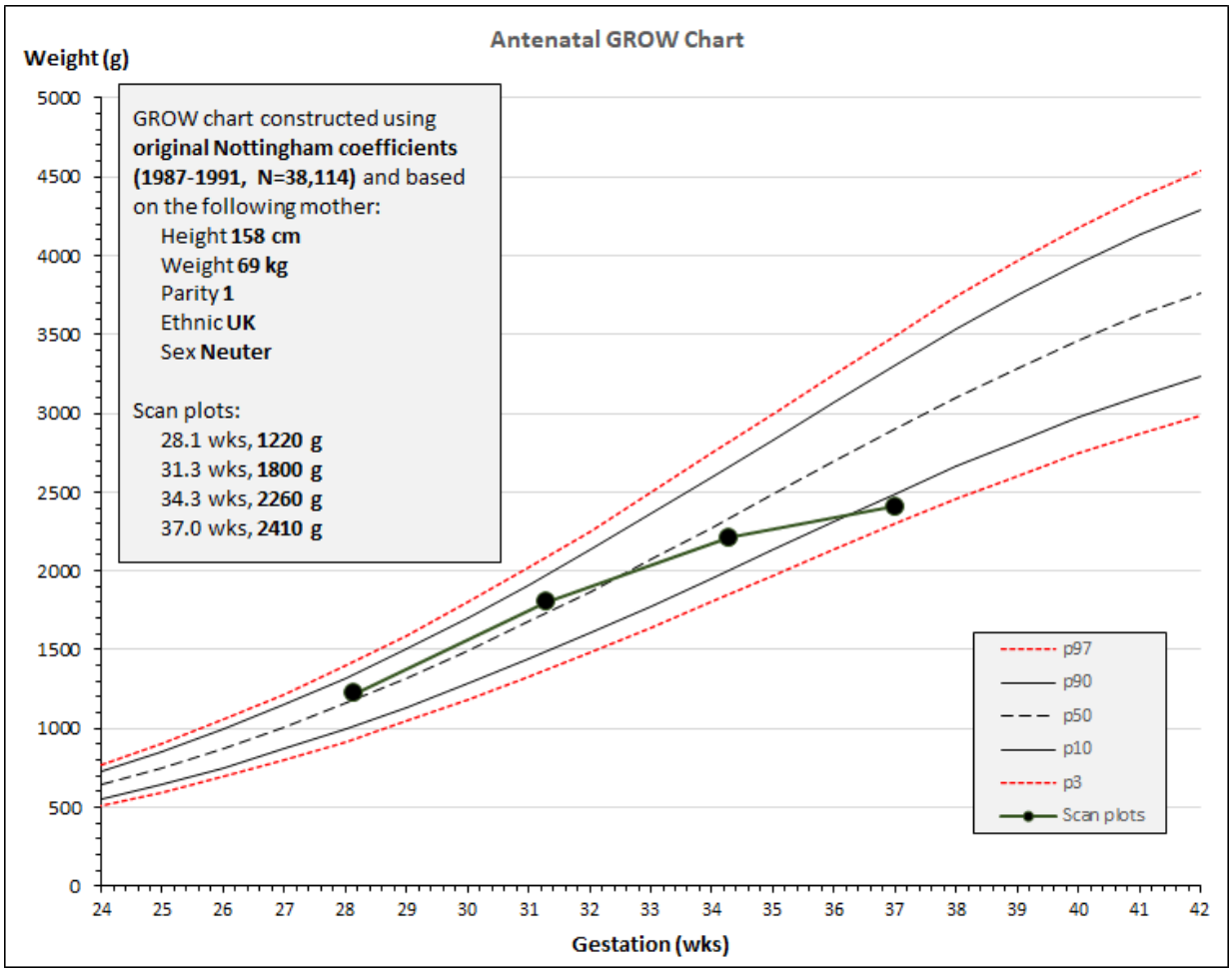


Figure 4 Antenatal GROW chart based on original Nottingham coefficients



Appendix A : Full publication list

Medical publications: Papers (reverse chronological)

The Growth Asessment Protocol: a major cause of declining stillbirth rates in the UK. Ultrasound Obstet Gynecol. 2020 Jul [cited 2020 Sep 23];56(1):117–9. https://onlinelibrary.wiley.com/doi/abs/10.1002/uog.22100	Gardosi J, Turner S, Williams M, Buller S, Hugh O, Francis A.
Customised birthweight standard for a Polish population. Arch Med Sci. 2020;16(1)	Kajdy A, Hugh O, Modzelewski J, Rabijewski M, Francis A, Gardosi J.
Customised birthweight standard for an Iranian population. The Journal of Maternal-Fetal & Neonatal Medicine. 2019 Nov 25;1-6	Nasri K, Hantoushzadeh S, Hugh O, Heidarzadeh M, Habibelahi A, Shariat M, Francis A et al.
Customised birthweight standard for a Slovenian population. J. Perinat. Med. https://doi.org/10.1515/jpm-2018-0219	Tanja Premru-Srsen, Ivan Verdenik, Barbara Mihevc Ponikvar, Oliver Hugh, Andre Francis, Jason Gardosi
Customized vs INTERGROWTH-21st standards for the assessment of birthweight and stillbirth risk at term. AJOG. 2018 Feb;218(2, Supplement):S692–9.	Francis A, Hugh O, Gardosi J.
Customized growth charts: rationale, validation and clinical benefits. AJOG, Feb 2018 https://doi.org/10.1016/j.ajog.2017.12.011	Jason Gardosi, MD, FRCOG; Andre Francis, MSc; Sue Turner, BSc, RM; Mandy Williams, MSc, RM
Optimising the International Classification of Diseases to identify the maternal condition in the case of perinatal death. BJOG. 2016 Aug 16. doi: 10.1111/1471-0528.14246.	Allanson ER, Tunçalp Ö, Gardosi J, Pattinson RC, Francis A, Vogel JP, Erwich J, Flenady VJ, Frøen JF, Neilson J, Quach A, Chou D, Mathai M, Say L, Gülmezoglu AM.
Application of ICD-PM to preterm-related neonatal deaths in South Africa and United Kingdom. BJOG. 2016 Aug 16. doi: 10.1111/1471-0528.14245.	Allanson ER, Vogel JP, Tunçalp Ö, Gardosi J, Pattinson RC, Francis A, Erwich J, Flenady VJ, Frøen JF, Neilson J, Quach A, Chou D, Mathai M, Say L, Gülmezoglu AM.

The WHO application of ICD-10 to deaths during the perinatal period (ICD-PM): results from pilot database testing in South Africa and United Kingdom. BJOG. 2016 Aug 16. doi: 10.1111/1471-0528.14244.	Allanson ER, Tunçalp Ö, Gardosi J, Pattinson RC, Francis A, Vogel JP, Erwich J, Flenady VJ, Frøen JF, Neilson J, Quach A, Chou D, Mathai M, Say L, Gülmezoglu AM.
Giving a voice to millions: developing the WHO application of ICD-10 to deaths during the perinatal period: ICD-PM. BJOG. 2016 Aug 16. doi: 10.1111/1471-0528.14243. [Epub ahead of print] No abstract available.	Allanson ER, Tunçalp Ö, Gardosi J, Pattinson RC, Vogel JP, Erwich J, Flenady VJ, Frøen JF, Neilson J, Quach A, Francis A, Chou D, Mathai M, Say L, Gülmezoglu AM.
Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. BJOG, 2014 Nov 26, doi: 10.1111/147 1-0528.13202	Hodgetts VA, Morris RK, Francis A, Gardosi J, Ismail KM
Association between reduced stillbirth rates in England and regional uptake of accreditation training in customised fetal growth assessment. BMJ Open. 2013 Dec 17;3(12):e003942. doi: 10.1136/bmjopen-2013-003942.	Gardosi J, Giddings S, Clifford S, Wood L, Francis A.
Maternal and fetal risk factors for stillbirth: a population-based study. BMJ. 2013 Jan 24;346:f108. doi: 10.1136/bmj.f108.	Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A.
The customized fetal growth potential: a standard for Ireland. Eur J Obstet Gynecol Reprod Biol. 2013 Jan;166(1):14-7. doi: 10.1016/j.ejogrb.2012.09.007. Epub 2012 Oct 12.	Unterscheider J, Geary MP, Daly S, McAuliffe FM, Kennelly MM, Dornan J, Morrison JJ, Burke G, Francis A, Gardosi J, Malone FD.
Association between pregnancy complications and small-for–gestational-age birth weight defined by customized fetal growth standard versus a population-based standard. The Journal of Maternal-Fetal & Neonatal Medicine. 2011 Mar;24(3):411–7.	Odibo AO, Francis A, Cahill AG, Macones GA, Crane P, Gardosi J.
The customised growth potential: an international research tool to study the epidemiology of fetal growth. Paediatr Perinat Epidemiol. 2011 Jan;;25(1):2---10	Gardosi J, Figueras F Clausson B, Francis A.
The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. Br J Obstet Gynaecol 2009;;116:1356---1363.	Gardosi J, Clausson B, Francis A.
Adverse pregnancy outcome and association with smallness for gestational age by customised and population-based birthweight percentiles. Am J Obstet Gynecol 2009;;201:28 e1---8	Gardosi J, Francis A.
A customized standard to assess fetal growth in a US population. AJOG 2009;;201:25 e1---7.	Gardosi J, Francis A.

Parity and smallness for gestational age. BJOG. 2009 Jul;116(8):1135-6; author reply 1136-7. doi: 10.1111/j.1471-0528.2009.02127.x.	Gardosi J, Francis A.
Association of smoking during pregnancy and fetal growth restriction: subgroups of higher susceptibility. Eur J Obstet Gynecol Reprod Biol. 2008 Jun;138(2):171-5. Epub 2007 Nov 26.	Figueras F, Meler E, Eixarch E, Francis A, Coll O, Gratacos E, Gardosi J.
Customized birthweight standards for a Spanish population. Eur J Obstet Gynecol Reprod Biol. 2008 Jan;136(1):20-4. Epub 2007 Feb 6.	Figueras F, Meler E, Iraola A, Eixarch E, Coll O, Figueras J, Francis A, Gratacos E, Gardosi J.
Cerebral palsy and restricted growth status at birth: population-based case-control study Br J Obstet Gynaecol;; 2008;; 115:1250---1255	Jacobsson B, Ahlin K, Francis A, Hagberg G, Hagberg, H, Gardosi, J.
The use of customised versus population-based birthweight standards in predicting perinatal mortality. BJOG. 2007 Oct;114(10):1301-2; author reply 1303. No abstract available.	Gardosi J, Clausson B, Francis A.
A customized birthweight centile calculator developed for an Australian population. Aust N Z J Obstet Gynaecol. 2007 Apr;47(2):128-31.	Mongelli M, Figueras F, Francis A, Gardosi J.
Audit of fundal height measurement plotted on customised growth charts MIDIRS Midwifery Digest 16:3 2006;341	Wright J, Morse K, Kady S, Francis A.
Classification of stillbirth by relevant condition at death (ReCoDe) - a population based cohort study Br Med J 2005;;331:1113---1117	Jason Gardosi, Sue M Kady, Pat McGeown, Andre Francis, Ann Tonks.
Intrauterine growth in twin pregnancies; Giorn. It. Ost. Gin. Vol. XXVII - n. 5 Maggio 2005	J Gardosi, S M Kady, A Francis
A customised birthweight centile calculator developed for a New Zealand population. Aust N Z J Obstet Gynaecol. 2004 Oct;44(5):428-31.	McCowan L, Stewart AW, Francis A, Gardosi J.
Restricted fetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand. 2004 Sep;83(9):801-7.	Frøen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pedersen B.
Excessive volume expansion and neonatal death in preterm infants born at 27-28 weeks gestation. Paediatr Perinat Epidemiol. 2003 Apr;17(2):180-6	Ewer AK, Tyler W, Francis A, Drinkall D, Gardosi J.
Perinatal outcome of SGA births defined by customised vs population-based birthweight standards. Br J Obstet Gynaecol 2001;108:830-4	Clausson B, Gardosi J, Francis A, Cnattingius S.
Customised fetal weight limits for antenatal detection of growth restriction. Ultrasound Obstet Gynecol, 2000;15:36-40	deJong CLD, Francis A, vanGeijn HP, Gardosi J.

Early pregnancy predictors of preterm birth: the role of a prolonged menstruation-conception interval. Br J Obstet Gynaecol 2000;107:228-37	Gardosi J, Francis A.
Controlled trial of fundal height measurement plotted on customised antenatal growth charts. Br J Obstet Gynaecol 1999;106:309-17	Gardosi J, Francis A.
Fetal growth rate and adverse perinatal events Ultrasound Obstet Gynecol 1999;13:86-89	DeJong CLD, Francis A, van Geijn HP, Gardosi J..
Controlled trial of fundal height measurement plotted on customised antenatal growth charts Br J Obstet Gynaecol, 1999;106:309-317	Gardosi J, Francis A.
Fetal weight gain in a serially scanned high-risk population Ultrasound Obstet Gynecol,1998;11:39-43	DeJong CLD, Gardosi J, Baldwin C, Francis A, Dekker GA, vanGeijn HP.
Gestational age and induction of labour for prolonged pregnancy. Br J Obstet Gynaecol. 1997 Jul;104(7):792-7.	Gardosi J, Vanner T, Francis A.
Comparison of second trimester biometry in singleton and twin pregnancies conceived by assisted reproduction techniques Br J Obstet Gynaecol; 1997:104:737-40	Gardosi J, Mul T, Francis A, Hall J, Fishel S.

Medical publications: Abstracts, Posters and Presentations (reverse chronological)

Stillbirth risk and small-for-gestational-age rate in subgroups according to maternal size: comparison of GROW, WHO and IG21 fetal growth standards. Ultrasound in Obstetrics & Gynecology. 202056(S1):19–19. https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.22245	Francis A, Hugh O, Gardosi J.
Slow growth defined by customized growth trajectory and adverse perinatal outcome. 8th International Fetal Growth Conference, Berlin Oct 2019	Andre Francis, Oliver Hugh, Jason Gardosi
Fetal growth trajectory assessed by customized limits and adverse perinatal outcomes. Bjog: An International Journal of Obstetrics and Gynaecology. 2019 DOI: 10.1111/1471—0528.	Francis A., Hugh O., Gardosi J.
The effect of mixed parentage on ethnic variation in birthweight. Bjog: An International Journal of Obstetrics and Gynaecology. 2019 DOI: 10.1111/1471—0528.15633	Hugh O., Francis A., Williams M., Gardosi J.
Fetal growth in twins: comparison of twin-specific STORK and singleton customized GROW charts. Bjog: An International Journal of Obstetrics and Gynaecology. 2019 DOI: 10.1111/1471—0528.15634	Francis A., Hugh O., Gardosi J.

Stillbirth risk and SGA rate in subgroups according to maternal size: comparison of GROW, IG21 and WHO fetal growth standards. Bjog: An International Journal of Obstetrics and Gynaecology. 2019 DOI: 10.1111/1471—0528.15636	Francis A., Hugh O., Gardosi J.
Prevalence of risk factors requiring serial ultrasound assessment of fetal growth according to new NHS England algorithm: fc1a.009. Bjog: An International Journal of Obstetrics and Gynaecology. 2016 Jun 1;123:8–9.	Francis A., Giddings S., Turner S., Gardosi J.
Effectiveness of ultrasound biometry at 34 – 36 weeks in the detection of small-for-gestational- age at birth. BJOG: An International Journal of Obstetrics and Gynaecology. 2016 Apr 1;123:86–7.	Francis A., Gardosi J.
Comparison of term optimal weight of babies of Indian origin born in India and England. BJOG: An International Journal of Obstetrics and Gynaecology. 2016 EP1a 079	N Aziz, E Fernandez, A Francis, J Gardosi.
Differences in optimal birthweight according to perinatal mortality risk in European vs non-European ethnic groups. RCOG World Congress 2016, Abstract 1916	Francis A. Williams M., Gardosi J.
Comparative analysis of SGA defined by customised GROW Charts and the UK-WHO neonatal weight charts to assess association with indicators of adverse pregnancy outcome. BJOG 2015 Apr 122	Francis A. Gardosi J.
Comparison of INTERGROWTH-21 based fetal weight standard with the INTERGROWTH-21 neonatal weight standard for defining SGA in a UK population. BJOG 2015 Apr 122;63-63	Francis A. Gardosi J.
INTERGROWTH-21 based fetal weight standards versus customized GROW standards and their ability to define SGA babies at increased risk of perinatal death. BJOG 2015	Francis A. Gardosi J.
Comparative analysis of SGA defined by customised GROW Charts and the UK-WHO neonatal weight charts to assess association with indicators of adverse pregnancy outcome**.** BJOG 2015	Francis A. Gardosi J.
Accuracy of ultrasound estimation of fetal weight at term Arch Dis Child Fetal Neonatal Ed 2011;96: Fa61	Francis A, Tonks A, Gardosi J
Creating a customized birth weight standard for Harris County's Hispanic population. Poster session. AJOG Vol 204 Issue 1 supplement S336 Jan 1 2011 DOI:https://doi.org/10.1016/j.ajog.2010.10.952	Nikolaos Zacharias, Sanaz Amini, Haleh Sangi-Haghpeykar, Andre Francis, Jason Gardosi
Maternal smoking cessation and fetal growth restriction. Poster session. AJOG Vol 201 Issue 6 supplement S78 Dec 1 2009 DOI:https://doi.org/10.1016/j.ajog.2009.10.191	Mandy Williams, Andre Francis, Jason Gardosi
Development of a customized fetal growth standard for a Mid-Western American population. AJOG Vol 201 Issue 6 supplement S137 Dec 1 2009 DOI:https://doi.org/10.1016/j.ajog.2009.10.365	Anthony Odibo, Andre Francis, George Macones, James Crane, Jason Gardosi

Antenatal detection of fetal growth restriction and stillbirth risk in mothers with high and low body mass index. AJOG Vol 201 Issue 6 supplement S209 Dec 1 2009 DOI:https://doi.org/10.1016/j.ajog.2009.10.428	Mandy Williams, Andre Francis, Jason Gardosi
Stillbirth in pregnancies of obese mothers is associated with increased risk of fetal growth restriction. AJOG Vol 201 Issue 6 supplement S223 Dec 1 2009 DOI:https://doi.org/10.1016/j.ajog.2009.10.470	Jason Gardosi, Mandy Williams, Andre Francis
Clinical causes of stillbirth associated with maternal obesity. AJOG Vol 201 Issue 6 supplement S223 Dec 1 2009 DOI:https://doi.org/10.1016/j.ajog.2009.10.471	Jason Gardosi, Mandy Williams, Andre Francis
Cerebral palsy is strongly associated with severe intrauterine growth restriction in term but not in preterm cases. AJOG Vol 189 Issue 6 supplement S74 Dec 1 2003 DOI:https://doi.org/10.1016/j.ajog.2003.10.044	Bo Jacobsson, Andre Francis, Gudrun Hagberg, Henrik Hagberg, Jason Gardosi
"Unexplained" stillbirths: An investigation of the clinically relevant conditions at the time of fetal death. AJOG Vol 189 Issue 6 supplement S158 Dec 1 2003 DOI:https://doi.org/10.1016/j.ajog.2003.10.354	Jason Gardosi, Sarah Badger, Ann Tonks, Andre Francis
Stillbirth and fetal growth restriction at preterm and term gestations in singleton pregnancies: A multivariate analysis. AJOG Vol 189 Issue 6 supplement S158 Dec 1 2003 DOI:https://doi.org/10.1016/j.ajog.2003.10.355	Jason Gardosi, Andre Francis, Sven Cnattingius
Neonatal deaths and fetal growth restriction at preterm and term gestation in singleton pregnancies: A multivariate analysis. AJOG Vol 189 Issue 6 supplement S158 Dec 1 2003 DOI:https://doi.org/10.1016/j.ajog.2003.10.356	Jason Gardosi, Andre Francis, Sven Cnattingius

Other publications: (chronological)

Advanced Level Statistics; Stanley Thornes (1st Edn 1978); 2 Edns	Francis A
Aspects of the Generalised Binomial and Negative Binomial Distributions (MSc dissertation); Brunel University (STR/24 1978)	Francis A
Business Mathematics and Statistics; Cengage Learning (2004); 1st Edn 1986; 6 Edns	Francis A

Quantitative Techniques and Information Technology; DPP (1986)	Francis A, Melville A J
Business Mathematics and Statistics (7th Edn); Cengage Learning (2014)	Francis A, Mousley B

Appendix B : Publications included in the thesis

Publication 1 US adverse outcomes (Gardosi and Francis)

Publication 2 Value of customised centiles (Gardosi et al)

Publication 3 Customised vs IG-21 International (Francis et al)

Publication 4 Customised fetal weight limits (De Jong et al)

Publication 5 ReCoDe (Gardosi et al)

Publication 6 Cerebral palsy and restricted growth (Jacobsson et al)

Publication 7 Risk factors for stillbirth (Gardosi et al)

Publication 8 Stillbirth rates reduction (Gardosi et al)