Constitutional birth weight determinants in customized birth weight centiles – a systematic review

Kristina B. Halvorsen

Kull V05

Prosjektoppgave for Det medisinske fakultet

Universitetet i Oslo

Veileder J. Frederik Frøen
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Abstract

Objective
Fetal growth restriction (FGR) has a strong negative influence on pregnancy outcome, and identifying this is of great importance in antenatal care. Serial measurement of fundal height is widely used as a screening tool to detect FGR pregnancies, despite lacking evidence of effectiveness in preventing perinatal deaths. One potential avenue of screening is customized growth centiles, adjusted for constitutional factors known to influence birth weight, and thus potentially improving the separation between the constitutionally small vs. the pathologically small baby. The aim of this literature review was to identify the current evidence for the development and use of such customized centiles for screening purposes.

Methods
Literature searches were conducted through PubMed, EMBASE, Medline and the Cochrane Databases in English literature after 1990. First, we searched for papers on what potentially constitutional factors affect birth weight. Second, what models had previously been developed for customized centiles. We then explored in depth the characteristics of potentially constitutional factors identified. Finally we searched for evidence of effectiveness screening with customized centiles to prevent adverse pregnancy outcomes.

Results and discussion
On the basis of articles found, we have isolated eleven factors being subject of a thorough analysis to decide whether or not to include them in future customized centiles. The factors are: Fetal sex, gestational age, mother and father’s height & weight, parent’s/siblings’ birth weight, parity, maternal age, maternal weight gain during pregnancy, smoking and ethnicity.

Conclusion
The following factors should be included in the development of customized birth weight and fetal growth centiles: Fetal sex, gestational age, maternal height and weight, the latter two after excluding the pathology of the extremes. Further, we have found that the effectiveness of customized centiles is promising, however still uncertain and randomized controlled trials are needed to assess their true evidence.
Introduction

Fetal growth restriction (FGR) is associated with a wide range of adverse outcomes, such as stillbirths, mortality during the first year of life, developmental problems in childhood and the risk of morbidity in adulthood (1-9). Among these, the close association between pregnancies affected by FGR and stillbirth is a challenge in antenatal care, as FGR-pregnancies constitute 30% to 60% of stillbirths (2, 3, 10, 11). Identifying pregnancies affected by FGR is therefore important, however difficult, as there is limited evidence of the effectiveness of the screening tools used today, such as serial ultrasound measures and symphysis-fundus height measures (SF-measures) (12-14).

Terms to describe small babies, including “low birth weight” (LBW) and “small for gestational age” (SGA) are popular, however insufficient as outcome measures for the purpose of screening for pathologically small babies. “LBW” does not include gestational age and is therefore inadequate. SGA is usually defined as being smaller than the 10th, 5th or 2.5 percentile for gestation, or below 2 SD from the mean of the population. However, a proportion of growth restricted fetuses can reach a weight above the 10th percentile, and consequently be missed. SGA will also include many small, healthy babies. The term fetal growth restriction (FGR) on the other hand, excludes the constitutionally small, healthy babies and includes the small fetuses suffering from pathological growth restriction and will consequently be used throughout this paper.

Although models to predict birth weight centiles after adjustment for constitutional factors have been well known, the potential avenue for screening by individually adjusted fetal growth curves was first introduced in our search period by Gardosi in 1992. He proposed a new method of adjusting for constitutional factors when predicting fetal growth and birth weight (15). Yet, this methodology has not been fully developed, and several birth weight determinants used by some authors have been questioned by others. Crucial to the understanding of customized centiles is the careful selection of variables to adjust for, and within what limits they can be used. One can only adjust for factors being truly constitutional as inclusion of determinants of increased risk of FGR as an adjusting factor would allow a fetus to be smaller than its potential without being identified as a risk pregnancy by screening. As an example, maternal smoking is a well known cause of growth restriction, and by including this variable in customized centiles, one would allow a pathological reduction of fetal growth and miss the opportunity of closer antenatal and obstetric follow-up and intervention. Also, while maternal size would obviously be among the primary constitutional birth weight determinants, there will be limits to its utility as both severe obesity and malnutrition is associated with poor outcome and abnormal fetal growth.

We define constitutional birth weight determinants as factors within the normal variation of maternal and fetal genetic and maternal body composition that are significantly associated with variation in birth weight of her offspring, but not associated with increased perinatal morbidity or mortality.

By adjusting for constitutional factors known to affect birth weight, the customized growth centiles can be used to outline a curve for the expected normal fetal weight gain given the potential of the individual pregnancy. The aim of this literature review is to identify constitutional factors influencing birth weight and fetal growth, and the potential for adjustment in customized centiles. Further, we aimed to review the evidence available for the use of such centiles.
Methods
The literature search was conducted through the PubMed database between June 9th and 12th 2009 and was limited by; human, English and 1990. All publications were screened by their titles by KBH and KG. The abstracts of selected articles were then studied, and the articles included in the review were read in full text. A “snowball” search strategy was used and related articles used as references in the identified articles were examined to capture articles not included in the original search. Details of the search strategy are listed in “Appendix: Search strategy”. We undertook four search strategies:

1) Potential constitutional birth weight determinants
   a. Purpose: To identify potentially constitutional birth weight determinants in literature.
   b. Limitations: To avoid excluding factors of potential interest, no restrictions were made in the search strategy to exclude risk factors for adverse pregnancy outcomes associated with FGR.
   c. Results: We found 1476 articles of which nnnn abstracts were reviewed 26 were included in this review. The identified determinants are presented in table 1.

Second, we conducted a search to reveal what research has been done on customized centiles. Repeat studies using already published methodology were excluded. We found 802 articles, 63 abstracts were read and seven unique methods for customized centiles were included. The seven models are presented in table 2.

Further, we aimed to explore the potential constitutional birth weight determinants found in search 1 and 2 to identify any associations with perinatal or infant mortality, as well as any potential limits of normality.

Literature on the effectiveness of customized centiles was searched for individually.

Throughout this article, the definitions used to describe different weight classes have been the following according to WHO. (16). Underweight: BMI < 18.50, normal range: BMI 18.50-24.99, overweight: BMI ≥ 25.00 and obesity: BMI ≥ 30.00.

Results
This part includes a presentation of the factors potential for adjustment and how they are related to fetal growth/birth weight and risk of adverse perinatal outcome. Also included is a discussion of whether or not each variable should be included for adjustment in customized centiles. Several of the factors from table 1 are not presented as their association with fetal growth is weak, uncertain or clearly pathological.

Fetal sex
It is well known that female infants weigh less than males at all gestational ages, yet they are more likely to survive (19) (53). Male gender is actually an independent risk factor for adverse pregnancy outcome and pregnancy complications. (54). However, there is a long and well incorporated tradition of adjusting for fetal sex when making growth centiles. As the differences in survival probably not are related to a low weight at birth, but rather the opposite (54), the differences in weight between male and female fetuses should still be adjusted for.
**Gestational age**

Gestational age is the single most important determinant of birth weight (19). It is therefore obvious that one cannot develop customized centiles without including gestation.

**Maternal height**

In a study designed to assess whether the smaller size of infants born to short mothers is associated with an increased risk of perinatal mortality, one concluded that slower fetal growth due to maternal short stature appears to be physiologic (55). The same conclusion is drawn in another paper, which does not find any effect of maternal height on perinatal mortality (56).

Others conclude that short maternal stature is associated with an increased risk of perinatal mortality (57, 58), and both perinatal death, prematurity and SGA (59). The adverse effect of a low maternal stature was found to be significant from heights < 150 cm, <149 cm and < 155 cm, respectively.

Studying literature on the effect of short maternal stature is a challenge as most papers include women in developing countries. The risk of confounding factors such as socioeconomic deprivation and lack of obstetric intervention and hospital care when the labor is complicated by CPD (cephalo-pelvic disproportion) is therefore high.

Only one study was found to be exploring the effect of a high maternal stature (60). It included 300 pregnancies of active-duty women in the military and did not find any adverse effect of a tall maternal stature (>65 inches = 165.1 cm) per se, but in the interaction between height >65 inches and weight gain exceeding 42 pounds (= 19.05 kg) there was an increase in pregnancy complications.

The literature found on the effect of maternal height on fetal growth and birth weight is heterogenic and of varying relevance. The basis of categorizing maternal shortness or tallness as having a pathological influence is therefore weak. However, we can be sure that within the normal height ranges, maternal height has a physiological influence (19), and should be adjusted for in customized centiles.

**Maternal weight / BMI**

Maternal weight at booking has a strong correlation to birth weight. (15). It is easily measurable and will always be registered at the first antenatal visit.

Maternal overweight and obesity are both associated with an increased risk of stillbirth and neonatal deaths. (61-64). Also to be mentioned is the fact that a high maternal pre-pregnancy weight increases the risk of other adverse reproductive health outcomes. (65-68).

Babies born to slim mothers weigh less than the babies of heavier mothers. But is that a matter of pathology? One group found that slower fetal growth due to low maternal pre-pregnancy BMI was physiologic. (55). Similarly a study showed that there was no statistically significant increased risk of stillbirth among underweight pregnant women. (64). Low BMI has, however, been associated with adverse pregnancy outcomes: Intrauterine growth retardation (IUGR), preterm birth and iron deficiency anemia. (68-72). One study from India found that low maternal weight (< 50 kg) was associated with an increased risk of perinatal death, prematurity and SGA. (59). However, 75% of the mothers included in this study had a weight < 50 kg, indicating maternal under nutrition and social deprivation. Such confounding factors could have influenced the results.

There is strong evidence that obesity increases the risk of stillbirth. This weight class should therefore not be included when adjusting centiles. More uncertainty among women with a low BMI makes it
hard to exclude a pathological influence, and this weight class should not be corrected for in customized centiles. For the normal weight ranges, however, one should adjust for the influence of maternal weight.

**Siblings and maternal birth weight**
There is evidence that the birth weight of a fetus’ mother (31) and siblings (17, 73) influences birth weight, with the latter having the strongest association. (17). An intergenerational effect has also been described, as maternal birth weight is an important risk factor for adverse reproductive outcome (29, 31, 74). As adjustment in customized centiles has to be with factors not associated with pathology, there is a risk of this happening if including this factor as one of the variables. If to be corrected for, one has to be sure that the pregnancies of the mother and/or sibling was without complications. Despite evidence of a strong correlation, there is a possibility for the inclusion of pathology, which we cannot allow. Furthermore, the uncertainty related to the mother’s accuracy in remembering her own birth weight and the birth weight of previous children makes the factors unsuitable for adjustment in customized centiles.

**Paternal height/weight**
Paternal anthropometric factors have an independent influence on a baby’s birth weight, with the father’s height probably having a stronger association than weight/BMI (27, 28). However, as they often will remain unknown, they are of less importance and relevance for adjustment in customized centiles.

**Parity**
Several studies have revealed an increased risk of fetal death in nulliparous women. (55, 75-80). Also found is an increased risk of hypertensive diseases, placental complications, IUGR and other adverse pregnancy outcomes.(75).

Low multiparity does not seem to be associated with an increased risk for the fetus. (75, 78).

Grand multiparity increases the risk of obstetric complications, neonatal morbidity and perinatal death. (77-80).

As there is an obvious conformity of an increased risk in pregnancies with nulliparous and grand multiparous mothers, this factor should not be corrected for when making customized centiles. This decision is in accordance with a French multicentre study. (81).

**Maternal age**
Several large studies have reported an increased risk of stillbirth with high maternal age. (21, 82-87). The risk seems to become significant in women over 35 years. (75, 78, 84, 86, 87).

One group found that teenage pregnancies (ages 15-19 years) are associated with an increased risk of stillbirth (88), while others have concluded that teenage pregnancies are, in contrast to high maternal age, more associated with neonatal death than stillbirth. (89). The latter can probably be explained by the fact that teenage pregnancies inhibit an increased risk of preterm birth. (77). The association between restricted fetal growth and teenage childbearing is more controversial. (90).

Both extremes of age inhibit an increased risk. Furthermore, the adverse outcomes related to age is a continuum rather than threshold effect, which would have impeded making an adjustment in only one age interval. The factor should not be included in the developing of customized centiles.
Maternal weight gain during pregnancy

Maternal weight gain during pregnancy clearly affects birth weight. However, the actual weight gain is unknown at the beginning of pregnancy when the centiles are made, thus the factor is irrelevant for customized centiles.

Smoking

Literature clearly shows that smoking in pregnancy significantly increases the risk of stillbirth and FGR. (76) (44, 75, 77). One paper argues that the increased risk can fully be explained by an increased incidence of compromised fetal growth and placental complications. (75).

Others show that even the exposure to environmental tobacco smoke reduces the mean birth weight by > 33 g and increases the incidence of birth weight < 2500 g by 22%. (45).

Apart from one paper (50), the authors of the other articles in table 2 have argued only to include constitutional factors in their centiles and have consequently not included smoking. We want to emphasize the importance of keeping pathology out of customized centiles designed to reveal the potential growth of a fetus. Smoking can therefore not be adjusted for when composing such centiles.

Ethnic origin

There are significant birthweight and mortality variations between ethnic groups. (19, 36, 37, 91, 92). The question is, however, whether the variations are caused by constitutional and/or environmental influences.

One paper found that ethnic Chinese infants born in the US, China and Taiwan, with their thorough differences in living- and socioeconomic standard, almost had an identical birthweight distribution. Ethnic Chinese newborns in general had a lower mean birth weight than ethnic white individuals. Still, it was evident that the Asian births including Chinese infants had lower rates of infant mortality than white infants (19). Similarly, Japanese infants, whose birth weights are similar to that of US black infants, have the lowest mortality rates in the world. (93). These results suggest that the differences are constitutional; however, as no correction has been made for size, one cannot draw this conclusion.

Even if the disparities in mortality often are linked to socioeconomic differences, it has been proven that the increased risk within selected ethnic groups remains after adjusting for known socioeconomic risk factors. (94).

The diversity in research on this field might suggest that both constitutional and environmental factors contribute to the differences in birth weight and perinatal mortality among different ethnic groups. Without being able to exclude the possible influence of pathology, one cannot correct for ethnicity when making customized centiles.

Evidence for customized centiles

After customized centiles were first introduced in 1992 (15), others have presented similar models, including those presented in Table 2 (10, 48-50, 52). It has been claimed that the centiles have improved the identification of babies not reaching their potential weight and hence being at increased risk of morbidity and mortality. (2, 10, 95-97). One paper concluded that babies being re-classified as SGA by customized standards compared to population based standards had an increased risk of stillbirth (OR = 4.52, 95% CI 2.47-8.14) and perinatal death (OR = 2.60, 95% CI 1.62-4.15). (10).

Also found is the tendency of the centiles to reduced the false positive diagnosis of FGR. (98), with the result of decreased anxiety and unnecessary referrals. There is still controversy regarding what factors to correct for. (81)
The effectiveness of customized centiles is promising, however still controversial and uncertain (99, 100). In a recently published review, the authors concluded that the evidence for the use of the centiles is good, but that further studies are needed to quantify their effectiveness in reducing adverse pregnancy outcome. (101). No randomized controlled trials have been done to investigate their true effectiveness.
Discussion

Through studying the literature, we have identified the factors we find safe adjusting for when developing customized centiles for routine use in antenatal care; fetal sex, gestational age, maternal height and maternal weight, the latter two after excluding the pathology of the extremes. A brief discussion of each factor was done in the results-part, but a few comments need to be added regarding some of the factors we have chosen to exclude.

The best gender and age-specific estimate of birth weight in a normal pregnancy, may be the birth weight of a previous healthy sibling from an uncomplicated pregnancy, seconded by the mother’s own birth weight if she was delivered healthy after an uncomplicated pregnancy (17). As such data are often not available for antenatal care (obviously in the primiparous), the second-best candidates will be estimates based on maternal size.

Some factors, such as maternal age and parity at the time of conception, are chiefly constitutional, but at the same time the extremes (teenage pregnancies, maternal age > 40 years, primiparity and grand multiparity) bring biological pathology and risk to the environment of the fetus. (33, 86, 102-106). As an example, the first born not only has a well-known lower birth weight, but equally higher morbidity and mortality, and there are no biological benefits for the fetus that would condone “accepting” low birth weight in the first born. Adjusting for these factors would therefore systematically increase the risk of adverse pregnancy outcome by impeding the ability of health professionals to identify FGR.

Ethnicity may be seen as almost an entirely constitutional factor from a genetic point of view, but the environmental and socioeconomic effects of belonging to an ethnic minority are often associated with significant pregnancy risk. (107-109). “Allowing” for at suboptimal fetal growth in a population already at risk of FGR may add further risk and health disparities by masking the pathological growth.

It must be the objective of future statistical analysis to decide how to include the factors where adjustment is only relevant within a defined interval of “normality”, i.e. maternal height and weight.

The effectiveness of customized centiles is promising, however still controversial and uncertain (99, 100). No randomized controlled trials have been done to investigate their true effectiveness, and this should be the priority of future research on this field.

Conclusion

The purpose of this study was to detect what factors influencing birth weight can potentially be used in customized centiles and to assess the evidence of their use. Through analyzing literature, we have concluded that the following factors should be included when developing customized birth weight centiles: Fetal sex, gestational age, maternal height and maternal weight, the latter two after excluding the pathology of the extremes. Further, the effectiveness of customized centiles is promising, however still uncertain and randomized controlled trials are needed to assess their true evidence.

Words and definitions

FGR - Fetal growth restriction
FHM - Fundal height measures
LBW - Low birth weight
SGA - Small for gestational age
IUGR - Intrauterine growth restriction
BMI - Body mass index
SF-measure - Symphysis-fundal height measurement

Appendix: Search strategy

Pub Med Search #1
Factors affecting birth weight

("Birth Weight"[Mesh] OR "birthweight*" OR "birth weight*") AND ("birthweight centile*" OR "birthweight standard*" OR "birthweight chart*" OR "birthweight curve*" OR "birthweight norms" OR "birthweight reference*" OR "birthweight distribution" OR "birth weight centile*" OR "birth weight standard*" OR "birth weight chart*" OR "birth weight curve*" OR "birth weight norms" OR "birth weight reference*" OR "birth weight distribution" OR "growth centile*" OR "growth standard*" OR "growth chart*" OR "growth curve*" OR "growth norms" OR "growth reference*" OR "growth distribution" OR "reference values"[Mesh] OR "normal values"[Mesh] OR "normal variation") AND (prepregn* OR pregnan* OR "pregnancy"[Mesh])

Limits: Human, English, abstracts

Number of citations: 1476

Pub Med Search #2
Individually adjusted centiles

Search #1 AND (custom* OR adjust* OR individual* OR correc* OR "Genetic Variation"[Mesh] OR constitution* OR factors)

Limits: Human, English, abstracts

Number of citations: 802

Pub Med Search #3
Potentially constitutional factors

Limits: Human, English

# 1: ("stillbirth"[MeSH Terms] OR stillbirth* OR "fetal death"[MeSH Terms] OR fetal death* OR "perinatal death*" OR "perinatal mortality" OR "neonatal death*" OR "neonatal mortality" OR "infant death*" OR "infant mortality") AND humans[MeSH Terms].

# 2 ("Maternal Age"[Mesh]AND #1

Number of citations: 2454
# 3 ("Maternal weight") AND #1
Number of citations: 107

# 4 ("Maternal height" OR “maternal stature”) AND #1
Number of citations: 71

# 5 (“gestational age”) AND #1
Number of citations: 4090

# 6 (Sex"[Mesh] OR "gender" OR "fetal gender" OR "fetal sex") AND #1
Number of citations: 449

# 7 ("maternal birth weight" OR "maternal t" OR "parental birth weight" OR "parental birthweight" OR "paternal birth weight" OR "paternal birthweight") AND #1
Number of citations: 423

# 8 ("primiparity" OR "parity"[MeSH]) AND #1
Number of citations: 1897

# 9 ("Ethnic Groups"[Mesh] OR "race") AND #1
Number of citations: 1740

**PubMed search #4**

**Effect of customized centiles**
(pregnant OR pregnancy OR antenatal OR perinatal) AND (custom* OR adjust* OR individual* OR correc*) AND (centiles OR charts OR curves) AND (effect OR controlled trial OR rct)

Number of citations: 104

**Cochrane search**

**Effect of customized centiles**
"customized OR individually adjusted OR adjusted and charts OR centiles OR percentiles OR curves"

Number of citations: 8

**Embase search**

**Effect of customized centiles**
((pregnant or pregnancy or antenatal or perinatal) and (custom* or adjust* or individual* or correc*) and (centiles or charts or curves) and (effect or controlled trial or rct)).

Number of citations: 59
**Medline search**

**Effect of customized centiles**

\[((\text{pregnant or pregnancy or antenatal or perinatal}) \text{ and} (\text{custom* or adjust* or individual* or correc*}) \text{ and} (\text{centiles or charts or curves}) \text{ and} (\text{effect or controlled trial or rct}))\].

Number of citations: 91
### Tables

#### Table 1: Factors influencing birth weight

<table>
<thead>
<tr>
<th>Factor</th>
<th>Potentially constitutional</th>
<th>Potential health determinant</th>
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</thead>
<tbody>
<tr>
<td>Gestational age (17) talbell i Bukowski, American college</td>
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<td></td>
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<tr>
<td>Fetal sex (18-20)</td>
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<tr>
<td>Maternal weight (18-20, 23, 24)</td>
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<tr>
<td>Ethnicity/race (19, 32, 34-41)</td>
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</tr>
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</table>

The following factors associated with birth weight were found but not deemed to represent constitutional birth weight determinants: Socioeconomic/sociodemographic context (40, 41), plurality (19), parity (18-20), maternal age (18-22), gestational weight gain (19)

| Smoking (1, 18, 19, 34, 35, 42-44)                                     | X                          |
| Environmental tobacco smoke (45)                                     | X                          |
| Alcohol drinking (19, 34)                                            | X                          |
| Substance use (35)                                                   | X                          |
The aim of this table is to show whether the factors have a potentially constitutional or a potential health determinant influence on birth weight. “Constitutional” is used to describe the fixed genetic influence on birth weight. “Potential health determinant” is used to describe environmental factors affecting mother and/or child having a health effect (positive or negative) but through not measurable confounding, for example socioeconomic influence. For factors clearly having a pathological influence on birth weight, one has not sought to delve into the literature, and only one or a few references are listed. For factors where the literature is inconsistent on whether there is a constitutional and/or health determinant influence, more articles are included.

Table 2: Studies found to have explored the use of customized birth weight and/or fetal growth centiles:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Gardosi (15)</th>
<th>Wilcox (48)</th>
<th>Sciscione (49)</th>
<th>Figueras (50)</th>
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