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Bryan S Richardson

Barbra de Vrijer

Hilary K Brown

Larry Stitt

Sheryl Choo

See next page for additional authors

Authors
Bryan S Richardson, Barbra de Vrijer, Hilary K Brown, Larry Stitt, Sheryl Choo, and Timothy R H Regnault

Gestational Age Impacts Birth to Placental Weight Ratio and Umbilical Cord Oxygen Values with Implications for the Fetal Oxygen Margin of Safety

Bryan S Richardson[1,2,3,4], Barbra de Vrijer[1,4], Hilary K Brown[5], Larry Stitt[1], Sheryl Choo[1], Timothy RH Regnault[1,2,4]

Departments of Obstetrics and Gynecology[1], Physiology and Pharmacology[2], and Pediatrics[3], and Lawson Health Research Institute[4], University of Western Ontario, London, Canada, and Interdisciplinary Centre for Health & Society[5], University of Toronto, Toronto, Canada

Short title: Gestational Age and Cord Blood Oxygen

Corresponding Author: Bryan S. Richardson, MD; Department of Obstetrics and Gynecology, London Health Sciences Centre, Victoria Hospital, 800 Commissioners Road E, London, Ontario, N6A 5W9

Email: brichar1@uwo.ca

Phone: 519-685-8500, ext 64926

ABSTRACT

Background: We determined the impact of gestational age (GA) from near term to term to post-term on birth/placental weight ratio and cord oxygen values with implications for placental transport efficiency for oxygen, fetal O_2 consumption relative to delivery or fractional O_2 extraction, and oxygen margin of safety.

Materials and methods: A hospital database was used to obtain birth/placental weight ratios, cord PO_2 and other information on patients delivering between Jan 1, 1990 and Jun 15, 2011 with GA > 34 completed weeks (N=69,852). Oxygen saturation was calculated from the cord PO_2 and pH data, while fractional O_2 extraction was calculated from the oxygen saturation data. The effect of GA grouping on birth/placental weight ratio, cord PO_2, O_2 saturation, and fractional O_2 extraction values, was examined in all patients adjusting for pregnancy and labor/delivery covariates, and in a subset of low-risk patients.

Results: Birth/placental weight ratio and umbilical venous O_2 values increased with advancing GA, supporting the conjecture of increasing placental transport efficiency for oxygen. However, umbilical arterial O_2 values decreased while fractional O_2 extraction increased with successive GA groupings, indicating that fetal O_2 consumption must be increasing relative to delivery.

Conclusions: Fetal O_2 consumption can be seen as ever 'outgrowing' O_2 delivery over the last weeks of pregnancy and leading to a continued lowering in systemic oxygen levels. While this lowering in oxygen may trigger feedback mechanisms with survival benefit, the 'oxygen margin of safety' will also be lowered increasing perinatal morbidity and mortality which appear to be hypoxia related.

KEY WORDS: gestational age; placenta; fetal oxygen; fetal growth

INTRODUCTION

Fetal oxygen levels are directly related to fetal O_2 delivery which is equal to the product of umbilical vein O_2 content times umbilical blood flow [1-3]. In turn, umbilical vein O_2 content will be impacted by maternal oxygen levels, utero-placental blood flow, placental barrier surface area/thickness and placental oxygen consumption [1-3]. Concurrently, fetal oxygen levels are inversely related to fetal O_2 consumption which is equal to the product of umbilical veno-arterial difference in O_2 content times umbilical blood flow, and thereby fetal growth as a major component of oxidative metabolism [1-3]. It is the relationship of O_2 delivery to the fetus and the rate of fetal O_2 consumption which ultimately determines fetal blood and tissue oxygen levels. Notably the equilibrium of these two factors changes as both increase developmentally through pregnancy to accommodate maternal supply and fetal-placental demand [3-8].

Studies in the ovine fetus show blood PO_2 and O_2 saturation to be lower near term than at mid-gestation, attributed to the greater increase in fetal O_2 consumption than in O_2 delivery with advancing gestation [3,6]. Human studies with cordocentesis likewise show a fall in cord blood PO_2 and O_2 saturation from mid-gestation to near term, although associated increases in hemoglobin over this time period will limit the actual decrease in O_2 content [7-10]. However, studies in the ovine fetus over the last weeks of pregnancy with repeated blood sampling in individual animals show mixed results with PO_2 and O_2 saturation either unchanged [3,11] or continuing to decrease [12,13]. These studies suggest that the slowing of fetal growth normally seen near term decelerates the increase in O_2 consumption until it matches the increase in O_2 delivery, resulting in normalization of fetal oxygen levels [3]; or while decelerating the increase in O_2 consumption this still

outpaces the increase in O_2 delivery with fetal oxygen levels continuing to fall [12,13]. Most human studies with cord blood sampling at birth over the last weeks of pregnancy show PO_2 and O_2 saturation to be unchanged, albeit with low patient numbers and with findings unadjusted for the confounding effect of pregnancy and labor covariates [9,14-16]. However, in a relatively large population-based study (18,250 patients), we showed that O_2 saturation values in the umbilical vein increase while those in the artery decrease from preterm to term to post-term, although findings were again unadjusted for covariates [17].

The study of fetal oxygenation in relation to gestational age can be further assessed through fractional O_2 extraction and the concept of 'oxygen margin of safety'. Fetal fractional O_2 extraction is the ratio between fetal O_2 consumption and O_2 delivery and thereby equal to the product of umbilical veno-arterial O_2 content difference divided by umbilical vein O_2 content [2,18]. Since O_2 content is directly proportional to the O_2 saturation values of blood, saturation can be used as a surrogate for content [3,17,19]. Changes in fetal O_2 consumption relative to delivery which are both actively regulated, will result in a consequential change in O_2 extraction. With advancing gestation if fetal O_2 consumption increases at a faster rate than O_2 delivery then fractional O_2 extraction will also be increased. Since umbilical artery O_2 content equals the product of umbilical vein O_2 content times (1 – fractional O_2 extraction) [18], gestation-related increases in fractional O_2 extraction will result in an increase in umbilical veno-arterial O_2 content difference and a drop in arterial oxygenation pending associated increases in venous oxygenation. The extent to which fractional O_2 extraction can increase before this lowering of arterial oxygenation becomes insufficient for maintaining O_2 consumption with

on-setting acidosis, is the ‘oxygen margin of safety’ as an indication of the oxygen reserve available to the fetus [2,18]. As such, the study of fetal oxygenation over the last weeks of human pregnancy has clinical implications should a fall in umbilical artery levels be confirmed, providing a mechanistic basis for the slowing in fetal growth and increase in perinatal morbidity and mortality which appear to be hypoxia related [20-23].

In the present study we examined associations between gestational age at birth and umbilical vein and artery PO_2 and O_2 saturation over the last weeks of pregnancy. We hypothesized that venous oxygen levels would increase reflecting developmental increases in placental oxygen transport capacity, while arterial levels would fall reflecting increases in fetal O_2 consumption relative to delivery as would fetal fractional O_2 extraction, with implications for the oxygen margin of safety. A large hospital database was utilized with information studied from patients delivering near term, at term, and post-term controlling for multiple pregnancy and labor/delivery covariates to better delineate the effects of advancing gestation. Birth to placental weight ratios have additionally been studied since this is often used as a proxy for efficiency in nutrient transport with optimal placental growth resulting in a larger infant rather than a larger placenta [4,24,25], and is known to change over the last weeks of pregnancy [24,26-28].

MATERIALS AND METHODS

The perinatal database of St Joseph’s Health Care, London, Canada, provides targeted information on all births that occurred at the hospital, with data prospectively entered by dedicated database personnel. During the period of this study, the hospital was the tertiary care facility for southwestern Ontario, serving a population of

approximately 1.5 million. The study population was formed based on the following inclusion criteria: all patients delivering between January 1, 1990, and June 15, 2011 when the delivery unit was closed and moved to London Health Sciences Centre; gestational age at birth greater than 34 completed weeks; and singleton, live-born and no major anomalies. The database was used to obtain the following information for this study population: gestational age at birth as the primary independent variable; birth weight, placental weight, and umbilical vein and artery blood gases/pH, as primary outcome variables; and maternal age, parity, pre-pregnant body mass index (BMI), smoking status, pregnancy complications, fetal sex, anesthetic use and delivery type, and non-reassuring fetal heart rate (FHR) pattern as indication for cesarean delivery as population characteristics and potentially confounding covariates. The study was approved by the XX Human Subjects Research Ethics Board (no. 112567).

Consistent with clinical practice, gestational age was derived from the last menstrual period or corrected based on ultrasonography measurements [19]. An electronic weight scale was used by nursing personnel to weigh infants immediately after delivery. Placentas were weighed with membranes and umbilical cord by nursing assistants, again using an electronic weight scale. Umbilical vein and artery blood was routinely sampled by nursing personnel immediately after delivery for all infants deemed to be viable [19].

Maternal pre-pregnant weight and height for determining BMI values were those reported by patients at their first prenatal visit and recorded in the patient`s antenatal record. Pre-pregnant BMI values were divided into the following categories: (1) underweight < 18.5, (2) normal weight 18.5 - 24.9, (3) overweight 25 – 29.9, and (4) obese

> 30 kg/m^2. Fetal size at birth was divided into the following birth weight categories based on birth weight percentile in relation to weeks of pregnancy attained at the time of delivery and using the fetal growth nomograms of Hadlock et al [29] as previously reported [30]: (1) small for gestational age (SGA), birth weight < 10th percentile, (2) appropriate for gestational age (AGA), birth weight ≥10th percentile and ≤90th percentile, and (3) large for gestational age (LGA), birth weight > 90th percentile. Maternal smoking was scored as being present with any sustained use after pregnancy was diagnosed. Maternal pregnancy complications included chronic hypertension, pregnancy-induced hypertension, gestational diabetes, and overt diabetes using standard clinical criteria for these.

Cases that met the inclusion criteria were divided into two patient populations: (1) all patients, and (2) low-risk patients, a group that excluded patients who smoked, had chronic or pregnancy-induced hypertension, gestational or overt diabetes, SGA or LGA infants, or delivery by cesarean section. Each patient population was studied independently and divided into three gestational age groups (1) near term, delivery from 35 0/7 to 36 6/7 weeks, (2) term, delivery from 37 0/7 to 40 6/7 weeks, and (3) post-term, delivery ≥ 41 weeks.

Data Acquisition, Calculations, and Statistical Analysis

Placental weights < 0.5th percentile and > 99.5th percentile were excluded to avoid including data from incomplete placental material (e.g. placenta previa/accreta) or pathologically enlarged placentas (e.g. hydropic placentas). Umbilical vein and artery PO_2, PCO_2, and pH values were “cleaned” with values < or > 3 SD from their respective means reviewed in relation to each patient`s individual values, and corrected if likely to

have been mis-entered (e.g. mis-placed decimal point, wrong blood gas/pH category), retained unchanged if extreme but plausible, (e.g. high PCO_2 values with low PO_2 and pH values), and excluded if extreme and implausible. Cord gas and pH values were then "validated" using the criteria of Westgate et al [31], with values excluded when deemed to be unphysiological with umbilical vein PO_2 < umbilical artery PO_2 or umbilical vein PCO_2 > umbilical artery PCO_2. When there was a high likelihood the same vessel was sampled twice, this was ascribed to the venous cord sample recognizing the ease of sampling the vein compared with the artery. Remaining umbilical vein and artery PO_2, PCO_2, and pH values < 0.5^{th} percentile and > 99.5^{th} percentile were additionally excluded, thereby removing extreme blood gas/pH values more likely to be reflective of pronounced intrapartum events (e.g. fetal asphyxia, maternal hyperventilation), and thereby less reflective of "pre-labor" values.

Umbilical vein and artery O_2 saturation values were calculated from respective PO_2 and pH values using the empirical equation of Hellegers et al [32]. We have confirmed this equation to be highly accurate for values > 20%, but to progressively underestimate measured values between 20% and 10%, with calculated values falling to zero thereafter [17]. Accordingly, this empirical equation was used for calculated values > 20% but corrected using a linear adjustment for calculated values < 20% and > 1%, and with calculated values < 1% arbitrarily set to 5%, recognizing that measured values > 5% will be underestimated and measured values < 5% will be overestimated. Fractional O_2 extraction values were then calculated from respective umbilical vein and artery O_2 saturation values as (vein O_2 saturation – artery O_2 saturation)/vein O_2 saturation.

The effect of gestational age grouping on birth weight, placental weight, birth/placental weight ratio, umbilical vein and artery PO_2, O_2 saturation, veno-arterial O_2 saturation difference and fractional O_2 extraction values was examined, along with the relationship to pregnancy and labor/delivery characteristics as potentially confounding covariates. Data are presented as percentages and means ± SD. Pregnancy, labor and delivery characteristics among the gestational age groups were compared using analysis of variance with post hoc Dunnett`s test for continuous variables and Chi squared tests with Bonferroni adjustments for categorical variables. Comparisons of birth/placental weight ratio and cord O_2 findings among the gestational age groups for all-patients were made using analysis of covariance adjusting for potentially confounding variables, and for low-risk patients were made using analysis of variance with no adjustment for any of the covariates. P values <.05 were deemed statistically significant. Term deliveries were the reference group for post hoc pairwise comparisons. The impact of maternal diabetes and fetal sex on the primary outcomes studied will be reported separately.

RESULTS

Characteristics of the Study Population

There were 69,852 patients meeting the study inclusion criteria of whom 4.8% delivered near term, 77.4% delivered at term, and 17.8% delivered post-term. Of these patients, 37,960 met the low-risk criteria of whom 3.6% delivered near term, 76.2% delivered at term, and 20.2% delivered post-term. The pregnancy and labor/delivery characteristics for all patients by gestational age grouping are shown in Tables 1 and 2, respectively, with the term patients as the reference group. The data for the pregnancy,

labor and delivery characteristics outlined were available for > 98% of patients, except for maternal BMI which was only available for 69% of patients largely because pre-pregnant weight and height were not collected in the first 3 years of study.

Birth Weight, Placental Weight, and Birth to Placental Weight Ratios

Birth weights were available for all but 4 of the 69,852 patients, while placental weights were available for 94.5% of patients after exclusions and missing data. Birth/placental weight ratios were likewise available for 94.5% of patients and are shown by gestational age group for the all-patient and low-risk patient populations in Tables 3 and 4, respectively, with the term patients as the reference group. For all-patients, birth/placental weight ratios showed a stepwise increase from 4.64±0.77, to 5.22±0.83, to 5.41±0.84, in the near term, term and post-term groups, respectively (all $p < .01$), indicating that birth weights were increasing in size relative to placental weights with advancing gestational age. For the low-risk patients, birth/placental weight ratios similarly showed a stepwise increase from 4.72±0.77, to 5.30±0.82, to 5.44±0.84, for the near term, term, and post-term groups, respectively (all $p < .01$), with all of these values notably higher than respective all-patient values, indicating that birth weights were increased in size relative to placental weights in low-risk vs all-patients over the latter part of pregnancy.

Umbilical Cord PO_2, O_2 Saturation, and Fractional O_2 Extraction Values

Umbilical vein and artery PO_2 were available for 95.2% and 86.7% of patients, respectively, after exclusions and missing data. Umbilical cord PO_2, O_2 saturation, veno-arterial O_2 saturation difference and fractional O_2 extraction values are shown by gestational age group for the all-patient and low-risk patient populations in Tables 3 and

4, respectively, with the term patients as the reference group. Advancing gestational age impacted cord oxygen values for all-patients, with venous PO_2 showing a stepwise increase from 27.1±6.9, to 27.5±6.5, to 27.7±6.2 mmHg ($p < .05$ and $p < .01$, respectively), while arterial PO_2 showed a stepwise decrease from 16.6±5.6, to 15.3±5.3, to 14.6±5.2 mmHg (all $p < .01$), in the near term, term, and post-term groups, respectively. The subgroup of elective cesarean section patients showed findings trending in the same directions with venous PO_2 increasing from 25.1±8.6, to 25.7±7.5, to 26.6±7.7 mmHg, and arterial PO_2 decreasing from 13.2±5.6 and 13.2±4.9, to 12.5±5.1 mmHg, in the near term, term, and post-term groups, respectively. However, none of these changes were significant due to the smaller sample size with these patients representing only six percent of the all-patient population. In the low-risk patients, venous PO_2 was unchanged at 28.1±6.4 and 28.0±6.1, and then increased at 28.3±5.9 mmHg ($p < .01$), while arterial PO_2 showed a stepwise decrease from 18.0±5.2, to 16.0±5.2, to 15.2±5.2 mmHg (all $p < .01$), in the near term, term, and post-term groups, respectively. Notably, all the low-risk PO_2 values were higher than respective all-patient values. Changes in O_2 saturation from near term to term to post-term were similar to that of PO_2, with umbilical vein values stepwise increased in all-patients ($p < .05$ and $p < .01$, respectively) although unchanged in the low-risk patients, while umbilical artery values were stepwise decreased in both of these patient populations (all $p < .01$). Accordingly, veno-arterial O_2 saturation difference and fractional O_2 extraction values were increased with successive gestational age groupings in both patient populations (all $p < .01$).

DISCUSSION

In this large population-based study, several pregnancy and labor/delivery characteristics were found to differ across the gestational age groups. Notably, near term mothers were more likely to be underweight or obese and had increased SGA and LGA infants, smoking, hypertensive disorders, and diabetes, with these higher risk pregnancies leading to increased elective and laboring cesarean sections and non-reassuring FHR for cesarean section. Conversely, post-term mothers were less likely to be underweight and had decreased LGA infants, smoking, hypertensive disorders, and diabetes. However, despite having lower risk pregnancies, they still had increased laboring cesarean sections and non-reassuring FHR for cesarean section. These findings are in keeping with those previously reported [30,33-36], although this is one of the largest single-center population-based studies with pregnancy and labor/delivery outcomes in relation to both near term and post-term births. Since these characteristic differences could impact birth to placental weight ratio and umbilical vein and artery oxygen values [19,37], their confounding effects were adjusted for when determining the effect of gestational age grouping for the all-patient analysis or limited by also studying a subgroup of low-risk patients.

Fetal weight for a given placental weight at birth reflects the balance between respective growth rates, providing a measure of efficiency in nutrient transport by the placenta and has been studied in relation to varying pregnancy conditions [4,19,24-28,37]. We [27] and others [24,26,28] have shown that birth weight relative to placental weight increases with advancing gestation in keeping with an increase in placental transport efficiency for oxygen as a primary determinant of fetal growth [19]. This increase

in oxygen transport is facilitated by well-known gestation-related changes in the placenta including growth of terminal villi and thinning of the trophoblastic layers [3,38,39]. The present findings of a stepwise increase in the birth/placental weight ratios from near term to term to post-term are consistent with previous studies in this area [24,26-28]. However, by controlling for adverse pregnancy conditions with the all-patient analysis and studying a sub-group of low-risk patients, it is likely that the conjecture of increasing placental transport efficiency for oxygen with advancing gestation is physiologically based rather than due to associated placental pathologies that underlie shortened gestational lengths [24]. Additionally, birth/placental weight ratios in the low-risk patient groups were all higher than respective values in the all-patient groups suggesting increased placental transport efficiency for oxygen as would be expected in these healthier pregnancies.

Umbilical vein PO_2 and O_2 saturation were overall increased with advancing gestation, although changes for low-risk patients were minimal. These values are directly related to placental oxygen transport with diffusion of dissolved oxygen from the maternal blood of the intervillous space across the syncytiotrophoblast-capillary endothelium to the fetal blood of the villi and will be impacted by placental barrier surface area and thickness, and consumption of oxygen [1-3,5]. Accordingly, the increase in vein oxygen can be accounted for by the gestation-related growth and thinning of the placental barrier surface area as noted, and possibly a decrease in placental barrier consumption of oxygen with the thinning of the trophoblastic layers. Conversely, umbilical artery PO_2 and O_2 saturation were decreased in a stepwise manner with advancing gestation in both the all-patient and low-risk patient populations. These values are directly related to umbilical vein oxygen and additionally umbilical blood flow, and inversely related to fetal O_2 consumption [1-3].

Since vein oxygen increases as shown and umbilical blood flow likely increases with the Doppler measured decrease in resistance indices over the last weeks of pregnancy [40], fetal O_2 delivery will be similarly increased. Accordingly, the decrease in arterial PO_2 and O_2 saturation likely reflect a greater increase in fetal O_2 consumption due to increasing energy costs for growth and maintenance of cellular ionic gradients [1-3], than in O_2 delivery. PO_2 and O_2 saturation values in the low-risk patient groups were all higher than respective values in the all-patient groups, further supporting the conjecture of increased placental transport efficiency for oxygen in these healthier pregnancies.

Fetal fractional O_2 extraction increased with each successive gestational age grouping in the all-patient and low-risk patient populations. Since fractional O_2 extraction is the oxygen consumed by the fetus as a fraction of that delivered, this increase indicates that O_2 consumption must be increased relative to delivery as similarly seen in the ovine fetus over the latter part of pregnancy [3,6]. This increase in fractional O_2 extraction is a result of an increase in the umbilical veno-arterial difference in oxygen levels dropping arterial PO_2 and O_2 saturation as shown and indicating that fetal systemic levels must also be decreased [18]. However, hemoglobin also impacts blood oxygen capacity and thereby systemic oxygen levels, and is known to increase in the fetus over the last half of pregnancy [41]. While cord hemoglobin values were not available for study, these can be estimated at 17.5, 17.9, and 18.1 g/dL for the near term, term and post-term all-patient groups, respectively, using mathematical modeling of reference ranges for hemoglobin in neonates [41] and respective gestational ages at delivery. Umbilical artery O_2 content can then be calculated using respective hemoglobin, PO_2, and O_2 saturation values [42], with estimated values at 7.1, 6.3, and 5.9 ml O_2/100ml for the near term, term and post-term

all-patient groups, respectively. Accordingly, umbilical artery O_2 content as a comprehensive measure of blood oxygenation can also be seen to decrease in a stepwise manner, supporting the conjecture of a progressive decrease in systemic oxygenation and providing a mechanistic basis for the slowing of fetal growth normally seen near term [3]. Further clinical relevance is seen in the randomized trials of labor induction versus expectant management for post-dates pregnancies [21] and patients at term [23], with expectant management resulting in increased cesarean delivery. This outcome might relate to more advanced gestational age with expectant management and thereby with lower fetal oxygen levels and tolerance for labor. Notably, the increased cesarean delivery in the post-dates trial was for non-reassuring FHR [21] which was also seen herein in the post-term group despite their lower risk pregnancies. Moreover, retrospective cohort study has shown that infant mortality rates at 39, 40, and 41 weeks` gestation are lower than the overall mortality risk of expectant management for an additional week [22], which is likely to be hypoxia related [20].

Study limitations include the extent to which labor and delivery affect cord O_2 findings, with pulse oximetry showing O_2 saturation to be marginally decreased through labor [43], although fetal scalp sampling shows PO_2 to be little changed until a marginal fall just before delivery with these values then comparable to umbilical artery values [44]. However, cord O_2 findings at birth will relate to pre-labor/delivery oxygenation and can be reflective of this if the sample size is sufficient and covariates controlled for with large population-based studies showing cord O_2 values to be lower in SGA infants [19,37] as similarly seen with cordocentesis prior to labor [8,10]. Oxygen saturation values were calculated from the umbilical cord PO_2 and pH data with a previously derived empirical

equation and, although highly accurate for values > 20%, will progressively underestimate measured values between 20 and 10%, with calculated values falling to zero thereafter [17,32]. We therefore corrected calculated values < 20% and > 1% using a linear adjustment which should be fairly accurate; however, re-setting calculated values < 1% arbitrarily to 5% which applied to 1.5% of the arterial values, is still likely to underestimate these values on average. While this underestimation will lead to a lowering of arterial O_2 saturation and increase in fractional O_2 extraction, this should not negate the significant effect of gestational age on these values which overall were in keeping with those we [17,19] and others [16] have reported. Additionally, the changes in oxygen values herein reported are small. However, arterial values will tend to normalize to the extent that growth is decreased as an oxygen consuming process in response to a lowering in fetal oxygenation [2,3], and the increases in perinatal morbidity and mortality which appear to be hypoxia related with advancing gestation are likewise modest [20-23]. Lastly, placentas were weighed with membranes and umbilical cord and no attempt was made to remove placental blood which could increase population variance. However, this weighing of placentas was consistently used and any increase in population variance should not bias the internal validity of results and negate the significant changes in birth/placental weight ratios observed in relation to gestational age.

The present findings extend those previously reported [17,24,26-28] now combining the placental and cord O_2 outcomes and studying a patient population of sufficient size controlling for multiple covariates and including a low-risk group to better delineate the effects of gestational age. We have demonstrated a gradual increase in birth weight relative to placental weight and an overall increase in umbilical venous O_2

values from near term to term to post-term. These findings support the conjecture of increasing placental transport efficiency for oxygen as a primary determinant of fetal growth facilitated by gestation-related changes in placental morphology [3,19,24,38,39]. However, umbilical arterial O_2 values were instead decreased while fractional O_2 extraction was increased with successive gestational age groupings indicating that fetal O_2 consumption must be increasing relative to delivery. Oxygen-sensing feedback mechanisms mediated by catecholamines and insulin have been proposed as a means of maintaining constancy of fetal oxygenation over the last weeks of pregnancy by slowing fetal growth and decelerating the growth in O_2 consumption until it matches the growth in O_2 delivery [3]. Accordingly, while the slowing of fetal growth normally seen near term is likely to decelerate the increase in O_2 consumption, this must still outpace the increase in O_2 delivery with umbilical arterial O_2 values and thereby fetal systemic oxygen levels continuing to fall. These findings are similar to those we [19] and others [45] have reported in growth restricted infants where the decrease in growth and therefore in size at birth was insufficient to result in normalization of umbilical artery O_2 values. Fetal O_2 consumption can thereby be seen as ever 'outgrowing' O_2 delivery over the last weeks of pregnancy and leading to a continued lowering in systemic oxygen levels from that seen earlier in pregnancy [3,6-10]. This lowering in oxygen levels may have survival benefit, triggering oxygen-sensing feedback mechanisms that facilitate pulmonary maturation and parturition in a time-related manner, as well as slowing fetal growth [2-5, 46-48]. However, the 'oxygen margin of safety' will also be lowered providing a basis for the increasing risk for stillbirth and infant morbidity and mortality which appear to be hypoxia related, from near term to term to post-term [20-23].

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CONFLICTS OF INTEREST

None declared

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Table 1. Pregnancy characteristics by gestational age groupings.

	Near Term 35-36 wks N=3,338	Term 37-40 wks N=54,084	Post-Term ≥ 41 wks N=12,430
Maternal age (yrs)	28.8±5.7**	29.1±5.4	28.6±5.2**
Parity	0.90±1.20**	0.94±1.09	0.76±1.02**
Maternal BMI	25.1±6.3**	24.7±5.6	24.8±5.3
BMI categories	**		**
Underweight (%)	7.6	5.7	4.3
Normal (%)	52.4	57.2	57.8
Overweight (%)	22.6	22.3	23.8
Obese (%)	17.4	14.8	14.2
Smoking (%)	13.7**	10.4	7.8**
Chronic HT (%)	3.7**	1.3	0.5**
PIH (%)	18.8**	10.2	4.6**
Gest diabetes (%)	5.9**	4.3	1.2**
Overt diabetes (%)	2.7**	1.0	0.0**
GA at delivery (wks)	35.7±0.5**	39.0±1.0	41.2±0.3**
Male fetal sex (%)	54.7**	50.8	52.0*

Data presented as percentages and means ± SD; * p <.05, ** p <.01, versus respective Term group. BMI = body mass index, HT = hypertension, PIH = pregnancy-induced hypertension, GA = gestational age.

Table 2. Birth, labor and delivery characteristics by gestational age groupings.

	Near Term 35-36 wks N=3,338	Term 37-40 wks N=54,084	Post-Term ≥ 41 wks N=12,430
Birth weight (g)	2,746±488**	3,444±477	3,723±453**
Placental weight (g)	608±145**	676±139	704±135**
Birth weight categories	**		**
SGA (%)	13.3	8.0	9.9
AGA (%)	72.2	81.4	84.2
LGA (%)	14.6	10.6	5.9
Anesthetic use	**		**
Regional (%)	68.7	73.3	79.1
General (%)	6.4	1.9	1.9
None/Other (%)	25.0	24.8	19.0
Delivery type	**		**
Vaginal (%)	75.7	82.2	82.6
Labor CS (%)	14.9	10.5	15.9
Elective CS (%)	9.4	7.4	1.6
NRFHR for CS (%)	4.4**	2.5	3.6**

Data presented as percentages and means ± SD; ** p <.01, versus respective Term group. SGA = small for gestational age. AGA = appropriate for gestational age, LGA = large for gestational age, CS = cesarean section; NRFHR = non-reassuring fetal heart rate.

Table 3. Birth/placental weight ratios, umbilical cord blood PO_2 (mmHg), O_2 saturation (%) and fractional O_2 extraction values in all patients.

	Near Term 35-36 wks N=3,338	Term 37-40 wks N=54,084	Post-Term ≥ 41 wks N=12,430
Birth/placental weight	4.64±0.77**	5.22±0.83	5.41±0.84**
Um vein PO_2	27.1±6.9*	27.5±6.5	27.7±6.2**
Um artery PO_2	16.6±5.6**	15.3±5.3	14.6±5.2**
Um vein O_2 saturation	59.7±17.2*	61.0±15.9	61.5±15.2**
Um artery O_2 saturation	29.6±14.3**	25.8±12.6	23.8±11.7**
Um v-a O_2 saturation	30.6±13.8**	35.4±14.2	37.7±14.3**
Fractional O_2 extraction	0.51±0.18**	0.57±0.17	0.61±0.16**

Data presented as means ± SD; * p <.05, ** p<.01 versus respective Term group adjusting for the effect of parity, smoking, chronic and pregnancy-induced hypertension, gestational and overt diabetes, infant sex, and maternal body mass index for birth/placental weight, and additionally for anesthetic use, delivery type and non-reassuring FHR for cesarean delivery for the O_2 measurements. v-a = veno-arterial.

Table 4. Birth/placental weight ratios, umbilical cord blood PO_2 (mmHg), O_2 saturation (%) and fractional O_2 extraction values in low-risk patients.

	Near Term 35-36 wks N=1,353	Term 37-40 wks N=28,920	Post-Term ≥ 41 wks N=7,687
Birth/placental weight	4.72±0.77**	5.30±0.82	5.44±0.84**
Um vein PO_2	28.1±6.4	28.0±6.1	28.3±5.9**
Um artery PO_2	18.0±5.2**	16.0±5.2	15.2±5.2**
Um vein O_2 saturation	63.1±15.1	62.9±14.8	63.2±14.2
Um artery O_2 saturation	33.0±14.4**	27.0±12.8	24.8±12.0**
Um v-a O_2 saturation	30.5±13.4**	36.0±14.2	38.4±14.3**
Fractional O_2 extraction	0.48±0.18**	0.57±0.17	0.60±0.17**

Data presented as means ± SD; ** p<.01 versus respective Term group unadjusted for any covariates. Low-risk = no smoking, hypertension, diabetes, small or large for gestational age, or delivery by cesarean section. v-a = veno-arterial.