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Narrative Review

Re-examination of the estimated average requirement for carbohydrate intake during pregnancy: Addition of placental glucose consumption

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A B S T R A C T

Evidence-based dietary reference intakes for nutrients in healthy individuals were last set in 2005 by the Institute of Medicine. For the first time, these recommendations included a guideline for carbohydrate intake during pregnancy. The recommended dietary allowance (RDA) was set at ≥175 g/d or 45%–65% of total energy intake. In the decades since, carbohydrate intake has been declining in some populations, and many pregnant women consume carbohydrates below the RDA. The RDA was developed to account for both maternal brain and fetal brain glucose requirements. However, the placenta also requires glucose as its dominant energy substrate and is as dependent on maternal glucose as the brain. Prompted by the availability of evidence demonstrating the rate and quantity of human placental glucose consumption, we calculated a potential new estimated average requirement (EAR) for carbohydrate intake to account for placental glucose consumption. Further, by narrative review, we have re-examined the original RDA by applying contemporary measurements of adult brain and whole-body fetal glucose consumption. We also propose, using physiologic rationale, that placental glucose consumption be included in pregnancy nutrition considerations. Calculated from human in vivo placental glucose consumption data, we suggest that 36 g/d represents an EAR for adequate glucose to support placental metabolism without supplementation by other fuels. A potential new EAR of 171 g/d accounts for maternal (100 g) and fetal (35 g) brain, and now placental glucose utilization (36 g), and with extrapolation to meet the needs of nearly all healthy pregnant women, would result in a modified RDA of 220 g/d. Lower and upper safety thresholds for carbohydrate intake remain to be determined, of importance as preexisting and gestational diabetes continue to rise globally, and nutrition therapy remains the cornerstone of treatment.

Keywords: carbohydrate, pregnancy, placenta, glucose, RDA

Introduction

Evidence-based DRI for nutrients in healthy individuals were last set in 2005 by the Institute of Medicine (IOM) Food and Nutrition Board [1]. These recommendations were justified based on the most current information at the time, set with the goal of mitigating chronic disease risk across populations in the United States and Canada. Previously, population nutrition recommendations for pregnancy focused mostly on adequate protein and micronutrient intake [2]. The 2005 recommendations included a guideline for carbohydrate intake during pregnancy for the first time, set at a minimum of 175 g/d or 45%–65% of total energy for the RDA [1]. Although the dietary reference intakes (DRI) apply to all pregnant women, they are used to inform specific nutrition therapy plans for individuals with preexisting and gestational diabetes. Now impacting a growing number of pregnant women globally, the International Diabetes Federation recently reported a doubling in the prevalence of preexisting diabetes in pregnancy over the last decade [3] and a global prevalence of gestational diabetes mellitus at 14% [4]. Gestational diabetes may actually affect ≥20% of pregnant individuals and their infants in some regions depending on diagnostic criteria [5].

Starting in 1990 [6], in the absence of an RDA for carbohydrates during pregnancy [2], the formative approach to the treatment of gestational diabetes mellitus (GDM) has been nutrition therapy rooted in carbohydrate restriction, then defined as <40% of energy intake [6–8]. For diabetes in pregnancy, treatment with nutrition is designed to meet maternal and fetal energy needs, blunt maternal postprandial glycemia, and mitigate fetal overgrowth [7]. Although adjunctive

Abbreviations: AMDR, acceptable macronutrient distribution range; CV%, coefficient of variation %; EAR, estimated average requirement; DRI, dietary reference intake; GDM, gestational diabetes mellitus; IOM, Institute of Medicine; RDA, recommended dietary allowance.

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treatment with insulin or oral hypoglycemics intensifies nutrition therapy, strict control of carbohydrate intake remains the cornerstone of management strategies for diabetes in pregnancy [7].

The minimum requirement for carbohydrate intake to support metabolic and fetal energy needs is reasoned to be based on the brain's glucose requirement, and glucose is its dominant fuel substrate [1]. Many persons, however, consume carbohydrates below 122 g/d within 3 mo before conception [9], below 100 g/d in periconception/early pregnancy [10], or below 175 g/d [11,12] during pregnancy. In some regions of the world, the mean population intake of carbohydrates is declining [13]. The RDA for carbohydrate intake during pregnancy accounts for both maternal brain and fetal brain glucose requirements extrapolated to set a guideline appropriate for 97%–98% of the population. Like the brain, however, the placenta is a highly dynamic organ that also prefers glucose as its dominant fuel substrate [14,15]. In fact, in vivo evidence now available demonstrates the rate and quantity of placental glucose consumption in humans [16]. Failure to account for placental glucose requirements may lead to an underestimate of carbohydrate needs during pregnancy. Combined with declining carbohydrate intake in some regions of the world, there is concern that some pregnant individuals will consume less than a healthy amount of carbohydrates and/or increase their intake of fat and protein to potentially unhealthy quantities.

In light of the availability of new information describing placental glucose utilization [16,17], the recent popularity of low-carbohydrate diets within and outside of pregnancy [10,11,18], the rise in maternal diabetes in pregnancy [3,19], and that the IOM recommendations for carbohydrate intake during pregnancy were set nearly 2 decades ago [1], the purpose of this paper is 2-fold. First, the physiologic rationale for the RDA for carbohydrate intake in pregnancy will be reviewed. Contemporary data will be applied to this rationale to re-evaluate the appropriateness of the recommendation. Second, the RDA will be re-examined to account for placental glucose needs based on recently published in vivo human measurements of placental glucose consumption [20]. We propose that placental glucose utilization be an important consideration for nutrition guidelines during pregnancy. Our overarching goal is to stimulate discussion and to inform future investigations that clarify safety thresholds for carbohydrate intake during pregnancy.

Rationale for the 2005 RDA Guideline for Carbohydrate Intake in Pregnancy: A Review

The estimated average requirement (EAR) for carbohydrate intake during pregnancy is based on the brain's requirement for glucose in nonpregnant individuals, with an addition of the fetal brain glucose requirement [1]. The physiologic rationale for each of the maternal and fetal components of the RDA is provided in Table 1, summarized here because most clinical guidelines or contemporary reports do not describe the full justification. The brain is recognized as an organ highly dependent on glucose as its preferred fuel substrate. Evidence to support this comes from early studies in canines and then humans, in which arteriovenous differences in carbon dioxide and oxygen showed a respiratory quotient of 1.0 [21,22]. Notably, the brain is able to metabolize glucose completely to carbon dioxide and water [1]. This dependency on glucose is driven by the selective permeability of the blood-brain barrier, specialized tissue with high expression of glucose transporters, GLUT-1 and GLUT-3, that facilitate glucose transport via a sizable blood-brain concentration gradient. This protective mechanism prevents neuroactive components in the blood (i.e., glutamate) from freely crossing the blood-brain barrier [23].

Although the brain is able to utilize ketoacids as fuel in times of nutritional challenges, such as starvation, the preferred and most efficient fuel substrate is glucose, which can be either endogenous or exogenous in origin. Although the IOM acknowledged [1] that survival is theoretically possible in humans with zero carbohydrate intake, and there is some agreement on this point [24], reproductive capacity with zero carbohydrate pregnancy was not addressed. It has been demonstrated in canines that zero maternal carbohydrate intake led to increased offspring demise by 3 days of life [25]. In humans, it was further justified by the fact that survival without carbohydrate intake requires a substantial shift in metabolism that is dependent on the

TABLE 1
Rationale for the original (2005) Institute of Medicine recommendation [1] for carbohydrate intake during pregnancy with physiologic justification

EAR nonpregnant adults	Fetal brain glucose utilization	Total EAR	Conversion to RDA
100 g/d - Brain weight is consistent across adults: 1.29–1.45 ± 0.02–0.03 kg (mean ± SD) - Adult brain O_2 consumption in the fasting state is 4.18 mL/100 g/min (1.45 kg brain weight) - Average brain glucose consumption in the fasting state is ~33 μmol/100 g brain weight/min, or ~8.64 g/100 g of brain weight/d (based on 1.45 kg brain weight) - Estimated brain glucose requirement: 87–112 g/d – 30 g glucose from obligatory protein turnover per glucose production from glycerol per day - 50–100 g/d prevents ketosis - ~36 g/d supplies glycolyzing cells (RBCs, WBCs, and renal medulla) - Coefficient of variation is 15% for adult brain glucose utilization - Therefore, 100 g/d of glucose consumption should supply CNS and glycolyzing cells without requiring glucose replacement by protein, ketoacids	35 g/d - Average newborn brain weight ~380 g - Assume a similar brain glucose consumption rate to adults (~33 μmol/100 g brain weight/min) - Brain glucose requirement at term based on above brain weight + adult glucose consumption rate (in the absence of ketoacid utilization) is 32.5 g/d (round to 33 g/d) - Assume the fetal brain can derive 30% of its energy from ketoacids if needed - Obligatory glucose requirement IF 30% of glucose from ketoacids is: 32.5 * 70% = 22.75 g or 23 g/d, similar to maternal-fetal transfer rate - Average maternal-to-fetal glucose transfer rate per day of glucose: 17–26 g/d (sheep) - Term fetus (3 kg) requires ~168 kcal/d - 33 g/d rounded to 35 g/d should supply fetal brain glucose fuel needs without requiring replacement by ketoacids (from the mother) - Assume a similar coefficient of variation for fetal brain glucose utilization as adults (15%)	135 g/d 100 g + 35 g = 135 g/d	175 g/d ([100 g + 35 g] * 15%) * 2 + 135 g = 175 g/d RDA = ([EAR × 15%] * 2) + EAR

EAR, estimated average requirement; RDA, recommended dietary allowance.
The EAR covers the nutritional carbohydrate needs of ~50% of the population, and the RDA covers the needs of 97%–98% of the population (Oxygen = O_2 ; Red blood cell = RBC; White blood cell = WBC; CNS = Central nervous system).

adequate availability of protein and fatty acids [1]. The EAR (which covers the carbohydrate needs of ~50% of a population) and the RDA (to cover needs of 97%–98% of a population) then, were set with the intention of preventing the need for supplementation of glucose with alternate fuel substrates [1]. In pregnancy, this is a particularly important consideration since, with advancing gestation and increased insulin resistance, maternal physiology is supported by fatty acids so that glucose can be preferentially shunted to the fetal-placental unit [7, 26], and further demands on maternal fatty acids could jeopardize maternal adipose tissue stores necessary to support lactation [2]. Furthermore, it is well documented that both the low and high extremes of protein intake are associated with fetal growth restriction [27], adding a further consideration unique to pregnancy if the protein is required for gluconeogenesis to support brain energy needs.

As shown in Table 1, the EAR for carbohydrate intake in nonpregnant adults is 100 g/d [1]. Physiologic factors considered included the average adult brain weight, which is remarkably constant across adults, and the brain's oxygen consumption rate. Further discussion included the average brain glucose consumption rate in the absence of requiring glucose supplementation by alternative fuels, and the estimated brain glucose requirement minus glucose supplied by obligatory gluconeogenesis. The threshold for ketosis and the glucose requirement for cells dependent on glycolysis for adenosine 5'-triphosphate production (red and white blood cells and renal medulla) were also considered.

The fetal brain glucose utilization component of the EAR for pregnancy, 32.5 g/d (~33 g/d) rounded to 35 g/d (Table 1) [1], was based on an average *adult* brain glucose consumption rate applied to the average newborn brain weight (380 g) [28], also fairly constant across infants. It was further assumed, however, that the fetal brain is able to derive 30% of energy from ketoacids if there is a glucose deficit. Thus, accounting for ketoacid utilization, the obligate-term fetus brain glucose requirement was calculated as 23 g/d. This estimate was within the known maternal-to-fetal glucose transfer rate shown in sheep (17–26 g/d), which was the best information available at the time [1]. In addition, the known caloric energy requirement of a term fetus at an average 3 kg birthweight was further considered. In the end, 33 g/d (rounded to 35 g/d) based on the average newborn brain weight-based calculation for glucose utilization was applied to the EAR. It was reasoned that maternal glucose intake of 35 g/d would assure adequate fetal brain glucose availability without requiring supplementation with ketoacids and would further provide glucose to support maternal brain needs without requiring ketoacids.

To calculate the RDA, the 15% interindividual coefficient of variation for the rate of adult brain glucose utilization was applied to both the maternal and fetal estimates. The EAR for carbohydrate intake during pregnancy, then, was 100 g + 35 g = 135 g/d. As seen in Table 1, the conversion of the EAR to the RDA was: ([100 g + 35 g]* 15%)*2 + 135 g = 175 g/d, where 2 times the interindividual coefficient of variation (CV) was added to the EAR to estimate the carbohydrate nutrient intake needs for 97%–98% of a population.

The RDA for Carbohydrate Intake during Pregnancy: Does 175 g/d Remain Appropriate?

The adult brain component of the EAR

The IOM in 2005 [1] used the best evidence available at the time of publication, some of which were published as early as the 1920s. More recently published data in the comprehensive review by Dienel [21] allowed us to evaluate if the RDA for carbohydrate intake during pregnancy remains appropriate (Table 2). Newer measurement techniques for brain energetics and metabolism, such as [^{13}C] glucose and magnetic resonance spectroscopy, ^{1}H-, and ^{31}P-magnetic resonance spectroscopy, support that the average brain oxygen consumption and cerebral metabolic rate is similar to estimates considered by the IOM, and show that based on an average brain weight of 1.4 kg, the brain consumes ~91 g glucose/d [21] (Table 2). Although actual variance around the mean, or a coefficient of variation, was not reported, we calculated the percent difference in brain oxygen utilization as ~24% across individuals and the percent difference in the brain glucose consumption rate as ~40% across individuals (Table 2). This suggests that the EAR of 100 g/d for carbohydrate intake remains appropriate and that the interindividual coefficient of variation of 15%, representing dispersion around the population mean, remains applicable.

The fetal brain glucose consumption component of the EAR

Historically, in vivo measurement of uteroplacental blood flow and fetal substrate utilization has been hindered in human models due to the inaccessibility of the placenta during gestation. In recent years, the 4-vessel sampling technique has been developed and refined [17], allowing for studies of placental physiology at the time of delivery by cesarean section. Briefly, on the day of delivery, after an 8-h fast and during a period of fetal quiescence, Doppler ultrasound is employed to measure blood flow volume on both sides of the placenta in the uterine artery and umbilical vein. Just after the incision for delivery, blood samples are drawn from the uterine vein and radial artery (as a surrogate for the uterine artery). Blood samples from the umbilical artery and vein are obtained immediately after delivery of the newborn and clamping of the cord but before delivery of the placenta [16]. The technique allows for the calculation of utero-placental arteriovenous and fetal venous-arterial differences in glucose transfer per liter of blood, suggesting uteroplacental uptake and fetal consumption, respectively. Consequently, biomarkers, exosomes, transfer of medication, and omics measures can be evaluated [17]. The maternal-fetal gradient, which indicates the transplacental transfer of glucose, can also be calculated [17].

It has been described that the placenta itself consumes ~1/3 of glucose taken up [29] and transfers ~2/3 to the fetus. Using the 4-vessel technique in 179 pregnant women, it was demonstrated that, in fact, 30% of glucose extracted from maternal blood was consumed by the placenta, while 70% was transferred to the fetus [20]. In a smaller cohort of 40 individuals, it was shown using the 4-vessel approach that the placenta extracted 6% of available glucose per liter of blood passing the placenta and that the fetus consumed ~10% of the glucose per liter of blood passing through the fetal-placental circulation [16]. These estimates provide the first more accurate in vivo human data describing maternal-to-fetal glucose transfer and fetal glucose uptake just before delivery.

Data generated using the 4-vessel approach allow for the reexamination of the fetal brain glucose consumption component of the EAR for carbohydrate intake during pregnancy. Although the 4-vessel data are not able to provide an isolated estimate of fetal brain glucose utilization, they do provide rates of whole-body fetal glucose utilization at term delivery (Table 2). Using these measurements, we converted fetal glucose utilization rates from μmol*min^{-1} to grams per day of carbohydrate intake to assess the appropriateness of the original 35 g/d estimates. Although estimates for fetal glucose utilization per kilogram of weight were reported, we applied the unadjusted whole-body rate for 2 reasons. First, while the fetal brain weight at term delivery is less variable across newborns (SD: 0.08–0.09 kg, males and females), total fetal weight is much more variable (SD: 0.46–0.47 kg) [28]. Ultrasound prediction of fetal weight can be variable by 20% [30],

TABLE 2
Rationale for the suggested update to the 2005 Institute of Medicine recommendation for carbohydrate intake during pregnancy

EAR nonpregnant adults[1]	Fetal brain glucose utilization[2]	Placental glucose consumption[3]	Total EAR	Conversion to RDA
100 g/d	35 g/d	36 g/d	171 g/d	222 g/d Round down: 220 g/d
- Range of average brain O_2 consumption in adults is ~3.3–4.2 mL/100 g/min (24% difference across the range) (21) - Based on 1.4 kg brain weight in adults, the brain consumes ~91 g glucose/d. - Cerebral metabolic rate for glucose: 0.25 μmol/g/min, range of 0.2–0.3 μmol/g/min or a 40% difference across the range (21) - Based on these more recent data, the original obligate brain glucose requirement appears to remain appropriate at 100 g/d	-Maternal-fetal glucose gradient: 23 mg/dL (20) Median fetal <u>whole-body</u> glucose consumption (20): 96.8 μmol * min^{-1} (52.7, 144.5) (median, first, and third quartiles) **<u>Median</u>**: 96.8 μmol/L* min = 17.4395 mg/L 17.4395 * 1440 min/24 h = 25,112.88 mg or 25.1g/d (round to **25 mg/d**) **<u>First quartile</u>**: 52.7 μmol/L* min = 9.4944 mg/L 9.4944 * 1440 min/24 h = 13,671.936 mg or 13.7 g/d (round to **14 g/d**) **<u>Third quartile</u>**: 144.5 μmol/L* min = 26.0331 mg/L 26.0331 * 1440 min/24 h = 37,487.664 mg or 37.5 g/d (round to **38 g/d**) - Based on these more recent data, the original obligate fetal brain glucose requirement appears to remain appropriate to cover fetal whole-body needs (third quartile)	Average placental weight (n = 179; mean ± SD): 617 ± 113 g (20) Placental weight ranges (36) (n = 98, 39 wks, Ireland) 10th centile: 489 g 50th centile: 630 g 90th centile: 836 g Range: 409–637 g (n = 21, Philippines) (37) Based on this, assume placental weight 617 + 113 (1 SD) = 750 g or 0.75 kg (20) -Placental glucose consumption adjusted for placental weight (20) was 51.4 μmol * min^{-1} * kg^{-1} [–65.8, 185.4] (median, first, and third quartiles) **<u>Median</u>**: 51.4 μmol/L * min * kg = 9.2602 mg/L 9.2602 * 1440 min/24 h = 13,334.688 mg 13,334.688 * 0.75 kg = 10,001.016 mg or **10 g/d** **<u>Third quartile</u>**: 185.4 μmol/L * min * kg = 33.4017 mg/L 33.4017 * 1440 min/24 h = 48,098.448 mg 48,098.448 * 0.75 kg = 36,073.836 mg or **36 g/d** Work in pregnant sheep demonstrates placental glucose consumption CV% of 20%–35% (38–40); thus, 15% is likely a conservative estimate Apply the same coefficient of variation (15%) and use the estimate from the third quartile for placental glucose consumption	100 g + 35 g + 36 g = 171 g/d	([100 g + 35 g + 36 g) * 15%] * 2 + 171 g = 222 g/d Round down: 220 g/d

EAR, estimated average requirement
The EAR covers the nutritional carbohydrate needs of ~50% of the population, whereas the RDA covers the needs of 97%–98% of the population.
[1] Contemporary measurements of glucose consumption support that the current EAR remains appropriate for both maternal and
[2] Fetal brain glucose requirements.
[3] Further data from recent in vivo measurements estimate human placental glucose consumption[3] are translated to grams per day of carbohydrate based on 1440 min in 24 h. Consideration of the placenta as an organ highly reliant on glucose as a fuel source would result in an upward adjustment of 45 g/d to the RDA for dietary glucose intake to cover the maternal brain and glycolytic cell function, fetal brain, and placental glucose consumption [46].

making actual fetal weight during gestation unknown. Second, the mean birthweight in the sample from which 4-vessel measures were collected was 3546 ± 443 g (mean ± SD; n = 179) [20]. This approximates the 95th percentile for estimated fetal weight at 37 weeks of gestation, according to the World Health Organization, allowing for a calculation applicable to the broader population [31].

Table 2 shows that the range of first to third-quartile rates of fetal whole-body glucose utilization was 14–38 g/d. Typically +2 SDs from the population mean for clinical norms determine an upper threshold of "normal" [32–34]. Because only the median with first and third quartiles was reported for whole-body fetal glucose consumption, applying the logic for clinical norms using the third quartile calculation results in 38 g/d. This suggests that the initial approximation of 35 g/d should more broadly cover fetal whole-body consumption. In summary, the original EAR of 100 g to support maternal brain glucose requirements, the interindividual CV for adult brain glucose utilization, and the estimate of 35 g/d for fetal brain glucose requirements (which actually supports whole-body fetal glucose utilization) appear to remain appropriate based on more recently generated measurements.

The Placenta is a Glucose-Consuming Organ

The placenta relies on the maternal-fetal glucose concentration gradient to transport glucose substrate to fuel uteroplacental and fetal glucose needs. In the 4-vessel data [20], the maternal-fetal glucose gradient was 23 mg/dL (Table 2). Like the brain [21,23], the placenta prefers glucose as its dominant energy substrate and remarkably provides a specialized transport system between mother and fetus similar to the blood-brain barrier. The placenta also demonstrates high expression of glucose transporters designed to facilitate transport into the placenta and then to the fetus [35]. Although the placenta can use alternative fuel substrates such as fatty acids [14, 15] and is capable of glycogenesis [15], it remains unclear if the placenta has the capacity for gluconeogenesis [20]. Therefore, it is reasonable that glucose requirements for placental metabolism and transfer to the fetus are provided from maternal glucose. Applying this rationale, we propose that because the human placenta is completely reliant on the provision of maternal glucose, this creates a situation where adequate carbohydrate intake to supply placental glucose consumption is potentially as essential as for the brain, in addition to other aspects of placental functions. Thus, placental glucose needs are an important consideration for the EAR and RDA for carbohydrate intake during pregnancy.

How much glucose does the placenta consume? Using the recently published 4-vessel data [20], we were able to translate the placental glucose consumption rate adjusted for placental weight to grams per day of carbohydrate intake. As seen in Table 2, the average (±SD) placental weight across 179 individuals [20] was 617 ± 113 g. Several recent reports of placental weights across international studies [36,37] support that a 617 g placental weight is consistent with other population means. If +1 SD is added to the placental weight, this represents the approximate 75th centile for placental weight across nearly 100 placentas in a recent report [36]. We, therefore, assumed a placental weight of 750 g (617 g + 113 g, or mean + 1 SD). Applying the placental glucose consumption rates from the 4-vessel data [20] (Table 2), the range in median and third quartile rates is 10–36 g glucose/d. Using logic for clinical norms [32–34], we suggest using the third quartile estimate (36 g) as the EAR for placental glucose consumption. Table 2 shows that this results in a new overall EAR of 171 g/d (100 g + 35 g + 36 g) to cover maternal brain, fetal brain, and placental glucose consumption needs.

For conversion to a new RDA, we also considered if it is appropriate to apply the interindividual CV of 15% (for adult brain glucose consumption) to the placental EAR. Unfortunately, variance estimates for placental glucose utilization were not reported with the 4-vessel data [20] because the data were nonnormally distributed. However, based on work in pregnant sheep demonstrating placental glucose consumption CV%s of 20%–35% [38–40], 15% is likely a conservative estimate, and we, therefore, applied it here. This would result in an upward adjustment of the RDA for carbohydrate intake during pregnancy from 175 g/d to 220 g/d (Table 2). This new EAR accounts for maternal (100 g) and fetal (35 g) brain glucose utilization and placental glucose consumption (36 g). When 2x the interindividual CV of 15% is applied ([171 g * 15%] * 2 + 171 g = 222 g/d, round down), 220 g/d becomes the RDA to supply adequate glucose without replacement by alternative fuels.

Discussion

Prompted by the availability of the 4-vessel data describing placental glucose utilization [16,17], the recent popularity of lower carbohydrate diets within and outside of pregnancy [10,11,18], the rise in maternal diabetes in pregnancy [3,19], and that the IOM recommendations for carbohydrate intake during pregnancy were set nearly 2 decades ago [1], we re-evaluated the EAR for carbohydrate intake during pregnancy. Contemporary measurements support that the original EAR for maternal (100 g/d) and fetal (35 g/d) brain glucose consumption remain appropriate. However, and importantly, the rationale for adequate provision of obligate maternal and fetal brain glucose needs was never extended to consider the glucose requirements of the placenta, an organ that appears to be as dependent on maternal glucose as the brain [14,15]. We, therefore, propose that placental glucose consumption be brought to the forefront of maternal nutrition considerations during pregnancy. Application of the most accurate and controlled measurements of in vivo placental glucose consumption available [20], with translation to grams of carbohydrate intake per day, suggests that 36 g/d represents an EAR for adequate glucose to support placental metabolism without replacement by other fuels. If the new EAR, then, is 171 g (100 g + 35 g + 36 g), this results in a modified RDA of 220 g/d for carbohydrate intake during pregnancy.

Both low and high extremes of carbohydrate intake during pregnancy are associated with fetal growth faltering [41], making upper and lower thresholds critical considerations for nutrition recommendations during pregnancy. The integrity of transplacental glucose transport depends on the maternal-fetal glucose gradient, where maternal glucose is higher than fetal concentrations. Maternal hypoglycemia decreases uteroplacental glucose uptake, and fetal growth slows [42]. Theoretically, then, maternal glucose intake below a lower threshold could jeopardize this gradient, affecting fetal growth. Messaging from social media and nonevidence based sources encourage periconceptual and pregnant women to consume low-carbohydrate diets [43]. It has been reported by a systematic review that the average carbohydrate intake across 126,242 pregnant women in developed countries was 269.1 ± 37.0 g/d, lower or borderline-lower than country-specific recommendations [44]. Although some reports [45] describe appropriate carbohydrate intake in individuals with type 1 diabetes (51% of total energy), others [9,10,12] describe that many periconceptual and pregnant women, including those with type 2 diabetes [11], consume low-carbohydrate diet patterns (<175 g/d [1] and/or <40% of total energy intake [6,46]) as a method to control glycemia and "improve" pregnancy outcomes [41]. However, it remains unclear if this practice

is appropriate to support the range of maternal and fetal metabolic needs [41].

In the only randomized controlled trial to date where pregnant persons with gestational diabetes were randomized to 135 g/d of carbohydrate intake (vs. 180–200 g/d), individuals were unable to meet the target of 135 g/d. Although they did achieve an intake of 165 g/d and birth weight, small-for-gestational age and large-for-gestational age were not different between groups, maternal intake of iron and iodine was lower, and neonatal head circumference was smaller [47]. Of concern is further evidence that linked very low carbohydrate intake during the periconceptual period to an increased risk of neural tube defects [10], an observation not explained by inadequate folic acid intake [9]. It is well documented that starvation [48] and restriction of total energy intake during pregnancy [49], including in very recent reports [41,50], are associated with offspring growth restriction and reduced head circumference. Hardy and colleagues [51] recently proposed that the intake of digestible carbohydrates was necessary during the evolution of the human animal as a critical energy substrate for the growing brain and particularly the human fetus. In support of this concept, epidemiological data from South Africa recently suggested that birth weight *z*-scores were higher during seasons when maternal carbohydrate intake was higher (compared to when it was lower) [52], and other evidence suggests that size at birth is coupled with variation in carbohydrate intake independent of total calories consumed [41]. On the other side of the spectrum, carbohydrate intake at >70% of total calories is associated with patterns of reduced fetal growth, even when adjusted for total energy intake [53,54] (discussed in [41]). Due to a paucity of data available at the time, the IOM was unable to address the upper limits for macronutrient intake adequately; thus, this component of the DRI requires clarification [1]. The upper and lower safety thresholds for carbohydrate intake during pregnancy remain to be determined.

The consistent increase in maternal obesity has changed the global landscape of pregnancy [7]. Although the 2005 IOM recommendation [1] of 175 g/d for carbohydrate intake during pregnancy appears to remain appropriate for the support of maternal and fetal brain glucose needs, this recommendation also never accounted for maternal obesity (Table 2). The original RDA was set at ≥175 g of carbohydrate/d [1] to account for 45%–65% of total energy intake as an acceptable macronutrient distribution range. The acceptable macronutrient distribution range is not a DRI recommendation but is offered for planning diet patterns associated with mitigated chronic disease risk while supporting essential nutrient intake [1]. For pregnant women with higher BMI (>30 kg/m^2), 175 g of carbohydrate intake per day does not meet the recommendation of 45%–65% for isocaloric energy intake. If the total energy intake to avoid weight loss in these individuals is ≥2500 kcal/d, 175 g of carbohydrate consumed accounts for ≤28% of energy intake (4 kcal/g/carbohydrate), far below the lower recommended threshold of 45% of total daily energy and well into the range of what is considered to be a low-carbohydrate diet pattern [55]. This deficit would intensify with increasing energy demands of pregnancy if consumption of 175 g/d is maintained and pregnant individuals ingest more energy with advancing gestation [56]. Often with lower carbohydrate intake comes lower total energy intake [57], both independently linked with fetal growth faltering patterns [41], and the safety of weight loss for individuals with obesity during pregnancy remains to be confirmed [58].

For pregnant women with diabetes, the IOM recommendations are often operationalized by highly skilled registered dietitians and certified diabetes educators into daily prescription meal plans that partition carbohydrate intake by meal and snacks to equal 175 g/d [59]. This means that for individuals with diabetes in pregnancy and BMI ≥30 kg/m^2, strict intake at 175 g/d favors carbohydrate intake below 45% of total energy. Nutrition guidelines for gestational diabetes globally remain inconsistent, demonstrate high bias, and present recommendations with low rigor and low applicability [60]. This inconsistency represents a research priority for the field.

There are several knowledge gaps we must recognize in this re-evaluation of the RDA for carbohydrate intake during pregnancy. Because the 4-vessel data account for both uterine and placental glucose consumption, the actual placental component cannot be isolated [20]. However, at least in sheep, most uteroplacental glucose consumption has been shown to be accounted for by the placenta [15]. It is also important to remember that the 4-vessel data represent fasting conditions only at a time of fetal quiescence just before delivery, and do not reflect glucose uptake during postprandial conditions or during physical activity, or during early gestation. It is a further limitation that several individuals in the 4-vessel data study demonstrated a negative placental glucose consumption, limiting us from calculating the first quartile estimate and potentially pulling the median to a lower value. Moreover, finally, the 4-vessel data do not represent persons with BMI ≥30 kg/m^2; the median (first and third quartiles) early pregnancy BMI was 22.3 kg/m^2 (20.9, 25.4), and the mean (±SD) gestational weight gain was 15.0 ± 4.7 kg. Although placental glucose consumption was not associated with maternal BMI [20], cardiac output increases in obesity [61], and this may modify the calculation of the uteroplacental blood flow measures upon which the rates of uteroplacental and fetal glucose consumption were based. This work highlights several questions for the field that require elucidation. The placental glucose requirements specific to maternal obesity require clarification. Furthermore, the lower and upper safety thresholds for carbohydrates during pregnancy remain to be determined.

In conclusion, we propose that placental glucose consumption be brought to the forefront of maternal nutrition considerations during pregnancy. To promote discussion, we have calculated a potential new EAR for a carbohydrate intake of 171 g/d that accounts for maternal (100 g) and fetal (35 g) brain glucose utilization, and now placental glucose utilization (36 g). With the conversion to the RDA, the modified recommendation becomes 220 g/d to supply adequate glucose without supplementation by alternative fuels. We acknowledge the importance of messaging to all pregnant women emphasizing high-quality carbohydrate intake, instead of simple sugars and processed starches, to meet the RDA guideline [7,62]. We further highlight the critical need to clarify lower and upper safety thresholds for carbohydrate intake during pregnancy. Doing so has broad applicability to pregnant women and offspring globally and specific applicability to nutrition therapy recommendations for individuals with preexisting and gestational diabetes.

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Author disclosures

The authors report no conflicts of interest.

Author contribution

The authors' responsibilities were as follows – TLH and PJR share equal responsibility for all parts of the manuscript. Both authors have read and approved the final manuscript.

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