Gestational Diabetes Prevalence at Moderate and High Altitude

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Abstract

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Background: High-altitude (HA) pregnancies have been associated with decreased glucose levels and increased insulin sensitivity versus sea level. Our objective was to determine if the prevalence of gestational diabetes mellitus (GDM) and the impact of demographic characteristics on GDM diagnosis differed at moderate altitude (MA) versus HA.

Methods: Using a retrospective cohort design, we compared women living at HA (>8250 ft) and MA (4000–7000 ft) during pregnancy. Exclusion criteria were as follows: multiple gestation, preexisting diabetes, unavailable GDM results, or relocation from a different altitude during pregnancy. GDM diagnosis was determined using Carpenter and Coustan criteria. Data were compared by *t*-test (continuous variables) or chi-squared tests (categorical variables). Univariate, multivariate, and stepwise regression models were used to assess the impact of various factors on GDM prevalence.

Results: There was no difference in GDM prevalence between altitudes in these populations; the relationship between altitude and GDM was nonsignificant in all regression analyses. At MA, maternal age, Hispanic ethnicity, body mass index (BMI), and gestational age (GA) at testing increased GDM incidence in univariate analyses. At HA, maternal age, Hispanic ethnicity, and multiparity increased GDM incidence in univariate analyses.

Conclusion: While GDM prevalence did not differ between MA and HA, the impact of maternal demographic characteristics on GDM risk varied by altitude group. Higher BMI and greater GA at testing increased the incidence of GDM at MA, but not at HA. Multiparity had an effect at HA, but not MA. These differences may represent subtle differences in glucose metabolism at HA.

Keywords: Colorado; gestational diabetes; high altitude; pregnancy

Introduction

WITHIN THE CONTEXT of human physiology, high altitude (HA) is generally defined as greater than 8250 ft or 2500 m above sea level. Worldwide, ~140 million people are permanent residents at altitudes greater than 2500 m

(Moore et al., 1998). In the state of Colorado, ~250,000 individuals reside above 8250 ft (Moore et al., 1998; United States Census Bureau, 2010).

The effects of HA on obesity and glucose metabolism have been previously investigated. In a cross-sectional dataset from the United States, both the prevalence of obesity (Voss et al.,

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2013) and the incidence of type II diabetes (Woolcott et al., 2014) were inversely correlated with the elevation of residence. Similar results have been demonstrated worldwide and reviewed previously (Woolcott et al., 2015). With respect to glucose metabolism, prior studies have shown that male and nonpregnant female HA residents had lower fasting glucose levels, improved glucose tolerance, and decreased postprandial glucose elevation (Braun et al., 1998; Krampl et al., 2001a; Castillo et al., 2007). In pregnancy, fasting plasma glucose levels at HA were decreased compared to women at sea level and decreased further with advancing gestational age (GA) (Krampl et al., 2001a, 2001b). Also, there is a higher insulin sensitivity in pregnancy at HA (Krampl et al., 2001b). Pregnancy outcomes are also impacted by the altitude of residence. For example, lower infant birth weights have been observed in both moderate (Waldhoer and Klebermass-Schrehof, 2015) and HA pregnancies (Jensen and Moore, 1997; Moore et al., 1998; Gonzales et al., 2009) compared to low-altitude pregnancies. Pregnancies at HA also show increased rates of preeclampsia (Palmer et al., 1999) and preterm birth (Gonzales et al., 2009).

Our objective was to investigate the prevalence of gestational diabetes mellitus (GDM) at moderate altitude (MA) and HA populations with the hypothesis that the prevalence of GDM would be reduced at HA compared with MA. We also used univariate, multivariate, and stepwise regression analyses to assess the impact of demographic factors on GDM prevalence.

Materials and Methods

Study design

A retrospective cohort design was used. The MA cohort was women living in the Denver metropolitan area, who received prenatal care through the University of Colorado Hospital clinics. These data were collected previously in a prospective manner as part of the Denver Perinatal Database (2005–2012). Validation of this database was performed (described in *Statistical analysis*). We limited our cohort to women delivering between 2010 and 2012 to have as comparable a time period as possible to the available HA records (see next paragraph). City of residence was reviewed to ensure that each case resided between 4000 and 7000 ft above sea level. The laboratory values used for GDM diagnosis (both 1- and 3-hour oral glucose tolerance tests when available) were also hand abstracted for each record in the MA cohort.

The HA cohort was composed of women who received prenatal care at a partner clinic, High Country Healthcare, in Frisco, Colorado (clinic altitude 9075 ft). These data were collected retrospectively for all women receiving prenatal care and delivering between 2012 and 2015. These were the only years of records available for this study cohort based on technical limitations. City of residence was recorded for all women and verified to be >8250 ft above sea level. We chose to not include women living between 7001 and 8250 ft above sea level in either cohort to keep the study cohorts discrete.

GDM status was determined using the standard two-step screening process. The serum glucose is checked 1 hour after a 50-g glucose load is given. If this value is greater than 135 mg/dL, those women subsequently undergo serial blood sampling, following 100-g glucose load with final GDM diagnosis based on the Carpenter and Coustan diagnostic criteria (American College of Obstetricians and Gynecologists, 2017). This GDM screening method was recommended universally to all patients as part of standard obstetrical care

for the cohorts studied, and unavailable data were typically due to a late transfer of prenatal care after the standard testing time (and thus no laboratory values available) or patient noncompliance with the recommended testing.

For both cohorts, exclusion criteria were multiple gestation, unavailable laboratory results for GDM diagnosis, GDM testing before 20 weeks gestation, evidence of type 1 or type 2 diabetes before pregnancy, or evidence that the subject changed altitude of residence during pregnancy (i.e., moved from out of state or relocated from HA to MA). Only one pregnancy per patient was included; if two pregnancies occurred in the timeframe of interest, the first pregnancy was used. Collected variables included the following: city of residence, maternal age at estimated due date (EDD), Hispanic or non-Hispanic ethnicity, maternal height, maternal prepregnancy or first trimester weight, parity, GA at GDM testing (the GA at the 1-hour test if normal or the 3-hour test when done), GDM testing values, third trimester hemoglobin value, maternal smoking status, GA at delivery, infant birth weight, infant gender, and mode of delivery. Body mass index (BMI, kg/m^2) was calculated from the maternal height and prepregnancy or first trimester weight. Altitude of residence was determined by reported city address. Parity was defined as nulliparous (no prior pregnancies past 20 weeks GA), primiparous (one prior pregnancy past 20 weeks GA), or multiparous (two or more pregnancies past 20 weeks GA).

Flow diagrams of the final study populations are presented in Figures 1 and 2. This study was approved by the Colorado Multiple Institutional Review Board (approval #13-3199).

Statistical analysis

The Denver Perinatal Database, from which the MA cohort was drawn, was validated by review of a subset of the charts meeting our study criteria ($n=333$). Hand-abstracted values were compared to the analogous variables in the database using Cohen's kappa testing for categorical variables and Lin's concordance correlation coefficient testing for continuous variables. The agreement was acceptable for all variables except GDM status (data in Results section) and therefore GDM test results were subsequently retrieved from each individual's patient chart. Demographic and pregnancy characteristics were compared between MA and HA cohorts by *t*-tests for continuous variables and by chi-square tests for categorical variables. (BMI and parity were treated as categorical variables in our

FIG. 1. Flow diagram for moderate-altitude cohort. GDM, gestational diabetes mellitus.

FIG. 2. Flow diagram for high-altitude cohort. DM, diabetes mellitus.

analysis.) Univariate logistic regression models were used to assess the impact of altitude, maternal age, ethnicity, pre-pregnancy BMI, parity, GA at GDM testing, and smoking status separately on GDM status. Multivariate and stepwise logistic regression models were used with these variables predicting GDM diagnosis to assess the effects in the presence of confounding. All models were run for the group as a whole (MA + HA) and for each altitude cohort separately. In all models, unavailable data were treated as missing; hence, the number of subjects analyzed for Tables 2–4 is less than total number of pregnancies presented in Figures 1 and 2 and Table 1 since the multivariate and stepwise logistic regression analyses required complete data for each subject. For all groups, stepwise analyses are not presented as these did not significantly change the results from those acquired with multivariate analyses. A $p < 0.05$ was considered statistically significant. All statistical analysis and data manipulation were carried out in Rv3.2.2.

Results

Validation of the Denver Perinatal Database showed the following levels of agreement: maternal age at EDD (0.99), maternal height (0.96), maternal weight (0.97), parity (0.98), ethnicity (0.87), GA at delivery (0.97), mode of delivery (0.99), birth weight (0.92), infant gender (0.95), maternal smoking status (0.93), and GDM status (0.09). These, except for the GDM status, were considered appropriate levels of agreement for the variables.

Data were analyzed for 2925 completed pregnancies at MA (Fig. 1) and 552 completed pregnancies at HA (Fig. 2). Maternal demographics and pregnancy characteristics for each cohort are shown in Table 1. For demographic characteristics, parity was not different between altitudes, but the HA group was slightly older, more likely to have a BMI $< 25.0 \text{ kg/m}^2$, more likely to be Hispanic, and less likely to use tobacco. For pregnancy characteristics, the HA cohort had a slightly earlier GA at delivery (~ 4 days), a lower birth weight (206 g), and a higher third trimester hemoglobin value compared to the MA cohort.

The mean glucose level obtained at the 1-hour glucose testing was significantly lower in the HA group, 110.8 versus 105.9 mg/dL (Table 1). The mean GA at GDM testing was 6 days later in the HA cohort, which corresponds to 27 weeks 5 days at MA and 28 weeks 4 days at HA. However, there was no difference in GDM between cohorts with a prevalence of 4.0% at both MA and HA. Altitude was not a significant predictor of GDM in univariate, multivariate, or stepwise (OR 1.20, 95% CI 0.74–2.03, data not shown) logistic regression analyses (Table 2).

In all subjects (Table 2), univariate analysis showed that greater maternal age, Hispanic ethnicity, higher maternal BMI (i.e., overweight or obese groups), and later GA at GDM testing significantly increased the odds of gestational diabetes. Specifically, per year of increase in maternal age, the

TABLE 1. DEMOGRAPHIC AND PREGNANCY CHARACTERISTICS

Characteristic	MA (n=2925) ^a	HA (n=552) ^a	p ^b
Maternal age (years) at EDD, mean (SD)	29.1 (5.2)	29.8 (5.8)	0.015
Altitude of residence (feet), mean (SD)	5377 (204)	9375 (430)	<0.001
Maternal BMI (kg/m ²), n, %			<0.001
BMI <20.0	103, 3.5%	57, 10.3%	
BMI 20.0–24.9	1569, 53.6%	322, 58.3%	
BMI 25.0–29.9	710, 24.3%	114, 20.7%	
BMI ≥30.0	543, 18.6%	59, 10.7%	
Parity, n, %			0.114
Nulliparous	1260, 43.1%	258, 46.6%	
Primiparous	959, 32.8%	181, 32.8%	
Multiparous	706, 24.1%	112, 20.3%	
Non-Hispanic ethnicity, n, %	2340, 80.0%	376, 68.1%	<0.001
1-hour GDM screening result (mg/dL), mean (SD)	110.8 (26.0)	105.9 (26.4)	<0.001
GDM diagnosis, n, %	118, 4.0%	22, 4.0%	1.0
GA at GDM testing (days), mean (SD)	193.9 (29.4)	199.9 (13.8)	<0.001
Third trimester hemoglobin (g/dL), mean (SD)	12.2 (3.8)	13.1 (1.0)	<0.001
Tobacco use in pregnancy, n, %	341, 11.7%	30, 5.4%	<0.001
GA at delivery (days), mean (SD)	275.6 (13.0)	271.9 (11.6)	<0.001
Infant birth weight (kg), mean (SD)	3.3 (0.6)	3.1 (0.5)	<0.001

^aAvailable sample size for each characteristic with the following exceptions (n for MA and HA groups, respectively): BMI (2877, 510); parity (2925, 551); ethnicity (2901, 510); third trimester hemoglobin (2710, 503); tobacco use (2921, 548); GA at delivery (2925, 542); and birthweight (2921, 536).

^bAnalyzed by: *t*-test for continuous variables or chi-squared tests for categorical variables.

BMI, body mass index; EDD, estimated due date; GA, gestational age; GDM, gestational diabetes mellitus; HA, high altitude; MA, moderate altitude; SD, standard deviation.

TABLE 2. UNIVARIATE AND MULTIVARIATE REGRESSION, IMPACT ON GESTATIONAL DIABETES MELLITUS IN ALL CASES, N=3324

Characteristic	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Altitude ^a	1.01 (0.65–1.65)	0.957	1.22 (0.75–2.06)	0.439
Maternal age at EDD	1.06 (1.03–1.10)	<0.001	1.11 (1.07–1.15)	<0.001
Maternal BMI (kg/m ²) ^b	1.72 (1.41–2.08)	<0.001	1.73 (1.41–2.13)	<0.001
Primiparous ^c	1.03 (0.69–1.54)	0.867	0.76 (0.50–1.15)	0.193
Multiparous ^c	1.19 (0.78–1.81)	0.413	0.45 (0.27–0.73)	0.002
Non-Hispanic ethnicity ^d	0.50 (0.35–0.73)	<0.001	0.45 (0.30–0.69)	<0.001
GA at GDM testing	1.03 (1.02–1.04)	<0.001	1.03 (1.03–1.04)	<0.001
Tobacco use in pregnancy	1.41 (0.85–2.25)	0.162	1.69 (0.97–2.82)	0.055

Included pregnancies are 2819 at moderate altitude and 505 at high altitude. Reference groups were ^ahigh altitude, ^bBMI <25.0, ^cnulliparous cases, and ^dHispanic ethnicity.

CI, confidence intervals; OR, odds ratio.

odds of GDM increased at 6%; and for each day later in pregnancy, the odds of GDM increased 3%.

In univariate analysis of the MA cohort (Table 3), maternal age, Hispanic ethnicity, higher BMI category, and a later GA at GDM testing increased the risk of GDM. There was a 6% increase in GDM per year rise in maternal age. Maternal BMI showed the strongest effect. The same characteristics remained significant in the multivariate and stepwise regressions, with multiparity and maternal tobacco use becoming significant as well.

In univariate analysis of the HA cohort (Table 4), maternal age, Hispanic ethnicity, and higher parity increased the risk of GDM. The effect of maternal age was slightly greater compared to MA (9% per year increase in maternal age). Multiparity showed the strongest effect. The only characteristic that remained significant in multivariate and stepwise analyses for the HA cohort was maternal age.

Discussion

This analysis found a GDM prevalence that was similar to that reported previously in Colorado (Dabelea et al., 2005; Bardenheier et al., 2015), but was not different between pregnancies in these MA and HA populations within the state. Adjusting for possible confounders did not change this result. Increased BMI and GA at GDM testing were significantly associated with GDM diagnosis at MA, but not at HA, suggesting that some GDM risk factors are related to altitude of residence. In our sample, the HA cohort was less obese and less likely to smoke, and this has been found in other studies as well (Voss et al., 2013). In 2011, the prevalence of diabetes and obesity in Colorado were both the lowest in the nation (Xu et al., 2014). This may suggest an

overall higher level of baseline health in individuals who live in Colorado, particularly at higher altitudes.

There were differences between our cohorts, which may limit the comparison of these groups (Table 1). Some differences are less likely to be clinically significant, such as maternal age at EDD with less than a year variance between groups. Other differences are to be expected based on study design (altitude of residence) and known physiologic effects associated with living at altitude. In agreement with other studies at HA, we observed an increased third trimester hemoglobin, a slightly earlier GA at delivery, and a decreased birth weight in our HA cohort (Jensen and Moore, 1997; Gonzales et al., 2009; Waldhoer and Klebermass-Schrehof, 2015). While the increased Hispanic ethnicity represented in our HA cohort impacted GDM prevalence in the univariate analysis, this did not remain significant in the multivariate and stepwise analyses for the HA cohort.

Prior studies of the effect of altitude on glucose metabolism have been conducted in populations that have lived at HA for millennia such as Bolivia and Peru (Krampl et al., 2001a, 2001b; Castillo et al., 2007; Zamudio et al., 2010), and have undergone natural selection for genetic traits that may affect aspects of glucose metabolism (Bigham et al., 2014; Moore, 2017). In these South American populations, multiple elements of glucose metabolism, including fasting (Krampl et al., 2001a, 2001b; Castillo et al., 2007) and postprandial (Castillo et al., 2007) glucose levels, arterial-venous glucose differential (Zamudio et al., 2010), and insulin sensitivity (Krampl et al., 2001b), have been shown to be affected by the altitude of residence. While populations have lived consistently at HA in Colorado for at least 200 years, it is unlikely that our cohort was enriched in multigenerational HA families or had the same, protective genetic traits as present in South American HA populations.

TABLE 3. UNIVARIATE AND MULTIVARIATE REGRESSION, IMPACT ON GESTATIONAL DIABETES MELLITUS AT MODERATE ALTITUDE, N=2819

Characteristic	Univariate OR (95% CI)	p	Multivariate OR (95% CI) ^a	p
Maternal age at EDD	1.06 (1.02–1.09)	0.003	1.11 (1.06–1.15)	<0.001
Maternal BMI (kg/m ²) ^b	1.86 (1.5–2.3)	<0.001	1.96 (1.56–2.47)	<0.001
Primiparous ^a	1.00 (0.65–1.53)	0.982	0.71 (0.45–1.11)	0.131
Multiparous ^a	0.98 (0.6–1.55)	0.93	0.33 (0.18–0.58)	<0.001
Non-Hispanic ethnicity ^c	0.55 (0.37–0.84)	0.004	0.49 (0.31–0.79)	0.002
GA at GDM testing	1.04 (1.03–1.04)	<0.001	1.04 (1.03–1.05)	<0.001
Tobacco use in pregnancy	1.58 (0.94–2.53)	0.071	1.82 (1.03–3.10)	0.032

Reference groups were: ^anulliparous cases, ^bBMI <25.0, and ^cHispanic ethnicity.

TABLE 4. UNIVARIATE AND MULTIVARIATE REGRESSION, IMPACT ON GESTATIONAL DIABETES MELLITUS AT HIGH ALTITUDE, N=505

Characteristic	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Maternal age at EDD	1.09 (1.01–1.18)	0.030	1.10 (1.01–1.20)	0.031
Maternal BMI (kg/m ²) ^a	1.16 (0.67–1.91)	0.581	0.97 (0.58–1.62)	0.916
Primiparous ^b	1.23 (0.39–3.76)	0.715	1.07 (0.32–3.57)	0.912
Multiparous ^b	3.13 (1.14–8.98)	0.027	1.81 (0.56–1.62)	0.326
Non-Hispanic ethnicity ^c	0.31 (0.12–0.74)	0.008	0.38 (0.13–1.07)	0.069
GA at GDM testing	1.01 (0.98–1.04)	0.535	1.01 (0.98–1.04)	0.656
Tobacco use in pregnancy	0.00 (– to –)	0.99	0.00 (– to –)	0.989

Reference groups were: ^aBMI <25.0, ^bnulliparous cases, and ^cHispanic ethnicity.

In addition to possible genetic differences between high-altitude populations in North and South America, it is also possible that there was no difference in GDM prevalence because the altitude difference was not great enough between our MA and HA groups. The previous HA glucose studies in Peru and Bolivia were conducted at >14,000 and 12,000 ft, respectively, versus sea level (Krampl et al., 2001a, 2001b; Castillo et al., 2007; Zamudio et al., 2010), and hence across a greater altitude gradient than available in Colorado. However, in this study, we did see differences in our HA cohort, particularly a higher third trimester hemoglobin concentration, suggesting that the difference in altitudes was sufficient to cause physiologic effects. Also, other work in Colorado has also shown physiologic differences across the altitude gradient studied here (Zamudio et al., 1995; Jensen et al., 1997; Palmer et al., 1999; Julian et al., 2008).

Although this study was not designed to fully assess glucose metabolism, we found that the plasma glucose levels after the 1-hour GDM screening test were lower in the HA group, in agreement with prior investigations of postprandial glucose levels in nonpregnant women and men at altitude (Braun et al., 1998; Castillo et al., 2007). It is possible that, while glucose metabolism is affected by the altitude of residence, these effects are not sufficient enough to affect the incidence of GDM diagnosis. An altered glucose metabolism could, in part, explain why maternal BMI was not a significant contributor to GDM at HA, but was significant at MA in this study. In addition, the influence of altitude on glucose metabolism may vary between men and women. The inverse relationship between altitude and diabetes mellitus shown in the United States was specific to males (OR 0.84, 95% CI 0.76–0.94) and not in women (OR 1.09, 95% CI 0.97–1.22) living at 1500 to 3500 m (reference group 0–499 m) (Woolcott et al., 2014).

In any study with nonsignificant results, the possibility of a type II error must be considered. Power analysis suggested that the sample sizes would be adequately powered to detect a 2% difference in GDM prevalence between cohorts. As the prevalence rates found were exactly the same, it is not possible to calculate the necessary sample sizes to show a difference in GDM prevalence between these populations. Therefore, a nonsignificant result is more likely to support a true nondifference.

The strengths of this study include the large MA database validated specifically for this study and our access to a unique HA patient population for addressing an original question. However, these databases also come with caveats. The MA pregnancy database was not collected after 2012 and HA records were not available before 2012. Thus, from the records available to us, we were not able to directly compare pregnan-

cies from the same years across a large population. It is possible that changes in GDM prevalence over time could have impacted our findings. While most reports do suggest an increase in the prevalence of GDM over time (Dabelea et al., 2005; Bardenheier et al., 2015; Lavery et al., 2017), this is not universal (DeSisto et al., 2014). Data specific to Colorado have shown that over a 5-year time span, the prevalence of GDM changed from 3.44% in 2005 to 4.25% in 2010 (Bardenheier et al., 2015), and another study showed that no significant change in GDM prevalence was observed between 2007–2008 and 2009–2010 (DeSisto et al., 2014). We therefore believe that the effect of this 3–5 year difference in the delivery years between our cohorts is minimal and does not completely explain the null result found. Our unique HA cohort also constitutes a study limitation as the number of pregnancies available for analysis was limited by the relatively small size of the population and records available, and the possibility that individuals choosing to live at HA may not be representative of populations living at lower altitudes. In addition, while we were able to assess the impact of several risk factors for GDM prevalence in our populations (maternal age, BMI, and Hispanic ethnicity), due to the limitations of the information available in the medical records, not all risk factors for GDM were able to be accounted for in this study.

Conclusion

The likelihood of GDM in any one woman will be influenced by a combination of factors that may influence glucose metabolism, such as physiological changes of pregnancy, genetic predispositions, her environment, and altitude of residence. While there was no difference in GDM prevalence between these MA and HA populations studied, there are several interesting observations worthy of further investigation. The lack of an effect of BMI or GA at testing on GDM diagnosis in the HA cohort may represent a subtle difference in glucose sensitivity at HA, which this study was not designed to detect. Future studies on the effects of HA residence on glucose metabolism in pregnancy could include comparison of fasting glucose levels, fasting insulin levels, or continuous glucose monitoring between altitudes. These types of studies would have the advantage of more explicit glucose measurements than the nonfasting oral glucose challenge test used for GDM diagnosis and possibility to determine insulin resistance. If no difference in these parameters between altitude groups emerged, then the previously observed alterations in glucose metabolism and insulin sensitivity during pregnancy (Krampl et al., 2001a, 2001b) would seem to be a specific adaptation to populations who have resided at HA for multiple generations.

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Author Disclosure Statement

No competing financial interests exist. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

References

- American College of Obstetricians and Gynecologists. (2017). Gestational diabetes mellitus. Practice Bulletin No. 180. *Obstet Gynecol* 130:e17–e31.
- Bardenheier BH, Imperatore G, Gilboa SM, Geiss LS, Saydah SH, Devlin HM, Kim SY, and Gregg EW. (2015). Trends in gestational diabetes among hospital deliveries in 19 U.S. states, 2000–2010. *Am J Prev Med* 49:12–19.
- Bigham AW, Julian CG, Wilson MJ, Vargas E, Browne VA, Shriver MD, and Moore LG. (2014). Maternal PRKAA1 and EDNRA genotypes are associated with birth weight, and PRKAA1 with uterine artery diameter and metabolic homeostasis at high altitude. *Physiol Genomics* 46:687–697.
- Braun B, Butterfield GE, Dominick SB, Zamudio S, McCullough RG, Rock PB, and Moore LG. (1998). Women at altitude: Changes in carbohydrate metabolism at 4,300-m elevation and across the menstrual cycle. *J Appl Physiol* 85:1966–1973.
- Castillo O, Woolcott OO, Gonzales E, Tello V, Tello L, Villarreal C, Mendez N, Damas L, and Florentini E. (2007). Residents at high altitude show a lower glucose profile than sea-level residents throughout 12-hour blood continuous monitoring. *High Alt Med Biol* 8:307–311.
- Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, and McDuffie RS. (2005). Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Program. *Diabetes Care* 28:579–584.
- DeSisto C, Kim S, and Sharma A. (2014). Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. *Prev Chronic Dis* 11:130415.
- Gonzales GF, Steenland K, and Tapia V. (2009). Maternal hemoglobin level and fetal outcome at low and high altitudes. *Am J Physiol Regul Integr Comp Physiol* 297:R1477–R1485.
- Jensen GM, and Moore LG. (1997). The effect of high altitude and other risk factors on birthweight: Independent of interactive effects? *Am J Public Health* 87:1003–1007.
- Julian CG, Galan HG, Wilson MJ, DeSilva W, Cioffi-Ragan D, Schwartz J, and Moore LG. (2008). Lower uterine artery blood flow and higher endothelin relative to nitric oxide metabolite levels are associated with reductions in birth weight at high altitude. *Am J Physiol Regul Integr Comp Physiol* 295:R906–R915.
- Krampl E, Kametas NA, Cacho Zegarra AM, Roden M, and Nicolaides KH. (2001a). Maternal plasma glucose at high altitude. *Br J Obstet Gynaecol* 108:254–257.
- Krampl E, Kametas NA, Nowotny P, Roden M, and Nicolaides KH. (2001b). Glucose metabolism in pregnancy at high altitude. *Diabetes Care* 24:817–822.
- Lavery JA, Friedman AM, Keyes KM, Wright JD, and Ananth CV. (2017). Gestational diabetes in the United States: Temporal changes in prevalence rates between 1979 and 2010. *BJOG* 124:804–813.
- Moore LG. (2017). Human genetic adaptation to high altitudes: Current status and future prospects. *Quat Int* 461:4–13.
- Moore LG, Niermeyer S, and Zamudio S. (1998). Human adaptation to high altitude: regional and life-cycle perspectives. *Yearb Phys Anthropol* 41:25–64.
- Palmer SK, Moore LG, Young DA, Cregger B, Berman JC, and Zamudio S. (1999). Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 m) in Colorado. *Am J Obstet Gynecol* 180:1161–1168.
- United States Census Bureau. (2010). 2010 Census Interactive Population Map. <https://www.census.gov/2010census/popmap> Accessed May 24, 2018.
- Voss JD, Masuoka P, Webber BJ, Scher AI, and Atkinson RL. (2013). Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States. *Int J Obes (Lond)* 37:1407–1412.
- Waldhoer T, and Klebermass-Schrehof K. (2015). The impact of altitude on birth weight depends on further mother- and infant-related factors: A population-based study in an altitude range up to 1600 m in Austria between 1984 and 2013. *J Perinatol* 35:689–694.
- Woolcott OO, Ader M, and Bergman RN. (2015). Glucose homeostasis during short-term and prolonged exposure to high altitudes. *Endocr Rev* 36:149–173.
- Woolcott OO, Castillo OA, Gutierrez C, Elashoff RM, Stefanovski D, and Bergman RN. (2014). Inverse association between diabetes and altitude: A cross-sectional study in the adult population of the United States. *Obesity (Silver Spring)* 22:2080–2090.
- Xu F, Mawokomatanda T, Flegel D, Pierannunzi C, Garvin W, Chowdhury P, Salandy S, Crawford C, and Town M; Centers for Disease Control and Prevention (CDC). (2014). Surveillance for certain health behaviors among states and selected local areas—Behavioral Risk Factor Surveillance System, United States, 2011. *MMWR Surveill Summ* 63:1–149.
- Zamudio S, Palmer SK, Droma T, Stamm E, Coffin C, and Moore LG. (1995). Effect of altitude on uterine artery blood flow during normal pregnancy. *J Appl Physiol* 79:7–14.
- Zamudio S, Torricos T, Fik E, Oyala M, Echalar L, Pullockaran J, Tutino E, Martin B, Belliappa S, Balanza E, et al. (2010). Hypoglycemia and the origin of hypoxia-induced reduction in human fetal growth. *PLoS One* 5:e8551.

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