INTRODUCTION

Women who conceive at high altitude face the simultaneous and synergistic physiological challenges of pregnancy and hypobaric hypoxia. Therefore, the maternal physiological adaptation to pregnancy is often impaired at high altitude. Compared to sea-level pregnancy, for instance, pregnancy at high altitude is associated with a lesser rise in uterine artery...
blood flow from a reduced increase in the diameter of the uterine arteries,\textsuperscript{1,2} and a reduced physiological fall in the maternal arterial blood pressure with advancing gestation.\textsuperscript{3} An incomplete physiological adaptation to pregnancy can result in sub-optimal placentation, reduced fetal oxygen delivery, and thereby increased risk of late pregnancy complications, including intrauterine growth restriction, low birth weight, and stillbirth.\textsuperscript{4} Women belonging to ancestry groups that traditionally reside at high altitude, like the Andean, have less attenuated cardiovascular adaptations to highland pregnancy, and hence better preserved fetal growth and reduced risk of later pregnancy complications.\textsuperscript{5-7} However, little is understood about the impact of ancestry on early pregnancy complications at high altitude, in particular the risk of miscarriage.

Miscarriage, or spontaneous abortion within the first 20 weeks of pregnancy, is a common phenomenon worldwide. The cumulative risk of miscarriage between weeks 5 and 20 has been estimated at 11%-22%.\textsuperscript{8} However, determining the true incidence of miscarriage in populations, including those at high altitude, is complex. Miscarriages often occur outside of medical settings and may be unreported and under-investigated. The most common known cause of early miscarriage is aneuploidy, with 50%-70% of miscarriages showing a chromosomal or genetic anomaly.\textsuperscript{9,12} Other miscarriages can be attributed to causes such as infection, maternal medical conditions, and uterine structural problems.\textsuperscript{13-15} However, at least 30%\textsuperscript{9,12} of miscarriages do not have an identifiable cause. Within this group, oxygen availability during early placentation may be a significant contributor.

An important factor modifying pregnancy adaptation at high altitude is the genetic background, or ancestry. Andean and Tibetan populations have been living at high altitude for >14 000 years and have historically been isolated, due to their location and difficulty of access, with little genetic admixture. Due to limited genetic admixture, Andean and Tibetan populations living at high altitude can reliably be grouped into genetically distinct ancestry groups. Andean ancestry confers protection against low birth weight,\textsuperscript{6,7,16} and Andean women have significantly higher uterine artery blood flow and oxygen delivery during high altitude pregnancy between weeks 20 and 36, compared with European women.\textsuperscript{5} Tibetan women are protected against low birth weight, preterm birth, and reproductive loss compared to Han Chinese women,\textsuperscript{17} as well as having significantly higher uterine artery flow velocity during high altitude pregnancy.\textsuperscript{18}

The early zygote is metabolically suited to a low oxygen environment,\textsuperscript{19} and increased oxygen tension can lead to oxidative stress. As the extravillous trophoblast invades the endometrium during early pregnancy, its proliferation creates plugs in the uterine and spiral arteries, preventing oxygenated maternal blood from bathing the placental villi during the first trimester.\textsuperscript{20} Evidence suggests that the extravillous trophoblast invasion is inhibited by hypoxia,\textsuperscript{21} and it is possible this occurs in pregnancy at high altitude. Therefore, a potential mechanism via which high altitude pregnancy could be linked to increased risk of miscarriage is through inadequate plug formation in the extravillous trophoblast. This would lead to exposure of the conceptus to higher than normal levels of oxygen from the maternal circulation at an inappropriate stage of development and the generation of oxidative stress.

We hypothesize that the effect of high-altitude hypoxia on the invasion of the extravillous trophoblast will vary between women of European and Andean women due to their differential adaptation to pregnancy. Therefore, women of European ancestry, who are least well physiologically adapted to pregnancy at high altitude, will be more vulnerable to miscarriage and, similar to Tibetan women, we hypothesize that maternal Andean ancestry will also be protective against miscarriage at high altitude.

As the global population expands, an increasing number of people live at high altitude, particularly those of non-Andean and mixed ancestry.\textsuperscript{22,23} Given the high incidence of adverse pregnancy outcomes in high altitude populations, it is imperative to understand the association between parental ancestry and miscarriage under the influence of hypobaric hypoxia. Such studies might aid in the identification of genetic markers or attributes that protect against miscarriage.

We aim to determine the influence of Andean ancestry on the risk of miscarriage at high altitude.

\section{Materials and Methods}

\subsection{Study design and location}

We retrospectively identified a cohort of women receiving prenatal and perinatal care at high altitude (3600-4130 m, La Paz, 1974-1985). Women were included if they had a complete reproductive history (gravidity and parity) recorded, and if they delivered at least one live-born baby at full term with no complications (Figure 1). Including only women who had experienced a successful pregnancy at high altitude ensures that (i) the cohort were long-term acclimatized residents and that (ii) included women did not have health or genetic issues that would prevent successful pregnancy at high altitude. Data were abstracted to electronic form by researchers with no knowledge of the study hypothesis.

5667 eligible women were identified in La Paz at four hospitals, of which 5386 met inclusion criteria (Figure 1). Ancestry was classified using surnames with methodology validated using gene markers.\textsuperscript{7,16} In Bolivia, most people use two surnames, one inherited from each parent, enabling detailed ancestry classification. Andean ancestry was classified as one or both surnames being Andean. European ancestry was classified as one or both surnames being foreign, and Mestizo ancestry was classified as surnames being mixed, or...
one Andean and one foreign surname. If there was only one surname recorded, ancestry was recorded as that. Hispanic surnames were classified as Mestizo rather than European unless there was clear evidence of them originating from Spain. Ancestry classification was carried out for the mother and the father separately. Maternal grandparental ancestry was also derived from the mother’s surnames.

Over the 10-year period of the data-set collection, women could have presented for more than one pregnancy. The analysis shows that a small number of women were included more than once in the cohort (99/5386, 1.8%), 84 women presented twice, and 15 women presented three times during the course of the data set collection. Removing these duplicates did not change any of the results substantively, and therefore each pregnancy was included and treated independently.

Of the four hospitals included in the study, 901 infants were born at two hospitals that were privately run and 4485 at two hospitals that were publicly funded. La Paz (3600-4150 m) is part of the largest metropolitan area in Bolivia, and in the 1980s it had a population of approximately 750 000. Although the altitude of each individual woman’s residence was not available in the data set, the altitude of residence has been taken to be >3600 m given the locations of the hospitals within the city and where the majority of the La Paz population is situated.

For each pregnancy, maternal and paternal surnames (2 surnames per adult; ancestry classified separately for mother and father), maternal age at delivery, total number of previous pregnancies, number of previous live births, and number of previous miscarriages were obtained from contemporaneous records. Women reported details to their nurses or doctors at the first appointment, who recorded them in the paper records. It was not possible to distinguish between spontaneous miscarriages and induced abortions; however, the number of induced abortions in the data set is likely to be low as abortion has been illegal in Bolivia since 1973, except in a few very specific circumstances. We also recorded birth outcomes: gestational age at delivery, birth weight, sex of baby, and birth length. Birth weights were transformed to gestational age and sex-adjusted centiles using the Intergrowth 21st standards. Reproductive history data for each woman were recorded at the time of the first presentation for maternity care. Age of menarche was not available for each individual woman, therefore, the average age of menarche in the population (13.1 years, no significant difference between groups) was used to calculate pregnancies per year of reproductive life.

The pregnancy rate per year of reproductive life was calculated by dividing the total number of times a woman reported ever being pregnant by years of reproductive life to date (age—age at menarche). The live birth to miscarriage ratio was calculated for all women who had at least one miscarriage, by dividing the number of live births by the number of miscarriages. While the number of pregnancies a woman experiences per year of reproductive life may be determined by multiple factors including personal choice, the outcome of the pregnancy is predominantly biologically determined in this context, where termination of pregnancy is illegal and difficult to obtain. Therefore, calculating the ratio of live births to miscarriages takes account of the social and cultural
choice that couples can exercise over the total number of pregnancies that they experience per year of reproductive life.

### 2.2 Statistical analyses

Data are reported as mean (95% CI) or as proportions with 95% CI. Characteristics were compared using Student’s *t*-test (2-tailed) for continuous variables, ANOVA for continuous variables with more than two groups (with Tukey’s HSD post hoc test), and Chi-squared tests for categorical variables. Multivariate logistic regression models were used to determine associations between ancestry and outcomes of interest. Mestizo ancestry was used as the referent group throughout. Mixed models were constructed with a random effect for the hospital of origin to minimize both possible socio-economic differences and hospital-to-hospital differences in maternity care. Models also included a fixed effect of maternal age to account for the increased likelihood of miscarriage with increasing maternal age. As the data set contained women who had not yet completed their reproductive lifespan, survival analysis was used to account for the different numbers of years at risk of each pregnancy outcome. An alpha level of 0.05 was used throughout.

All data analysis was performed using the R statistical software package version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Local Ethics Committee of the Bolivian Institute for High Altitude Biology (Consejo Técnico, Instituto Boliviano de Biología de Altura, IBBA, Universidad Mayor de San Andrés, La Paz, Bolivia; Resolución No. 004/2004). Data were analyzed by IG and CA.

### 3 RESULTS

Andean women experienced their first live birth at younger ages (*P* < .001; Table 1), although this difference may not be
clinically relevant. Andean women experienced significantly more pregnancies and live births ($P < .001$) than Mestizo women, and European women experienced significantly fewer ($P < .001$; Table 1). Andean women experienced fewer miscarriages than Mestizo and European women ($P < .001$; Table 1).

Andean women had significantly longer gestations ($P < .01$) and European women significantly shorter gestations ($P < .001$, Table 1) than Mestizo women. Andean women delivered babies that were heavier than those born to Mestizo women ($P < .001$), which in turn were heavier than those born to European women ($P < .001$; Table 1). These differences persisted after adjustment for gestational age and the sex of the baby. There was no difference in the sex ratio between ancestry groups.

Andean women experienced their first live births on average 2 years younger than Mestizo or European women (Figure 2, $P < .001$). Andean women experienced more pregnancies per year of reproductive life (Figure 3A; $P < .001$). About 30% of the total cohort had ever experienced miscarriage; 20% prior to their first live birth. Andean women were 24% less likely to have experienced a miscarriage prior to their first live birth than either Mestizo or European women (OR 0.76; CI 0.62-0.90, $P < .001$). Andean women had a significantly higher ratio of live births to miscarriages than women of Mestizo or European ancestry (Figure 3B; $P < .001$).

We also assessed the impact of the woman’s parental ancestry (maternal grandparental ancestry) on live birth to miscarriage ratio. There were insufficient women of European origin for whom the ancestry of both of her own parents could be identified. We, therefore, compared the influence of maternal grandparental ancestry only in women whose parents were both known to be of either Andean or Mestizo origin. Using women with one Andean (and one Mestizo) parent as the referent, women with two Andean parents had a significantly higher live birth to miscarriage ratio (Figure 3C; $P < .001$) than women with one or no Andean parents.

Using univariate analysis, the woman’s partner’s ancestry also has a significant impact on the live birth to miscarriage ratio (Andean v. Mestizo $P < .001$; European v. Mestizo $P < .01$; Table 2). However, there was a high concordance between the ancestry of each woman and her male partner. When the ancestry of each parent was considered as an independent variable, the independent effect of paternal ancestry on live birth to miscarriage ratio became non-significant (Table 2). Mothers of both Mestizo ($P < .001$) and European ancestry ($P < .001$) were significantly more likely to experience additional miscarriages per live birth than women of Andean ancestry, independent of their male partner’s ancestry (Table 2).

**DISCUSSION**

We show, for the first time, a significant impact of maternal ancestry on the risk of miscarriage at high altitude. Andean women pregnant at altitudes >3500 m are more likely to have live births than women of either Mestizo or European ancestry. Having more maternal grandparents of Andean ancestry increased the live birth to miscarriage ratio. European women at high altitude experienced a lower ratio of live births to miscarriages compared to women of other ancestry groups. Women of European origin also have fewer pregnancies overall per year of reproductive life at high altitude, which may reflect either cultural differences or increased difficulty in conceiving at high altitudes.

In contrast to maternal ancestry, paternal ancestry did not have a significant independent impact on pregnancy success. The fact that maternal but not paternal genetics has a strong influence on pregnancy success implies that the relative improvement in high-altitude reproduction in Andean women might be due to better maternal physiological adaptation to pregnancy at high altitude rather than advantageous fetal genetics.
There are many possible reasons why pregnancies in Andean women at high altitude are less likely to end in miscarriage than those in European women. Andean women tend to reproduce earlier, and maternal age is a major factor in determining reproductive success\textsuperscript{27,28} However, the ancestry effects within our data persist despite adjustment for maternal age, and when reproductive success is adjusted per year of reproductive life. It may be the case that Andean women are culturally better adapted to life at high altitude, for example with different lifestyles and/or dietary patterns. We are unable to capture all of these potential influences within the available data set. However, it may also be the case that Andean women have favorable genetic adaptations, selected through thousands of years of residence at altitudes $>3500$ m. At high altitude, Andeans have significantly higher levels of catalase and superoxide dismutase (SOD) in blood and plasma than Europeans\textsuperscript{29}.

This increased availability of antioxidant enzymes may protect the Andean conceptus from oxidative stress derived from the chronic hypobaric hypoxia of pregnancy at high altitude. Further, in early pregnancy, low oxygen tension is required to minimize exposure of the conceptus to reactive oxygen species\textsuperscript{30} Reduced protection from maternal oxygen due to possible impaired extravillous trophoblast plugging coupled with low levels of antioxidant enzymes could mean that the European conceptus is exposed to more oxidative stress early in pregnancy and thereby at higher risk of miscarriage. There is significant evidence that chronic hypoxia can promote oxidative stress and impact on embryonic and fetal development\textsuperscript{31,32} Some recent studies have found that both Tibetans and Andeans have ancestry associated single nucleotide polymorphisms in genes such as PRKAA1, EDNRA and NOS2 related to the hypoxia-inducible factor (HIF), hemoglobin concentration,
uterine artery diameter and metabolic homeostasis,33-36 all of which are likely to contribute to reproductive success at high altitude.

A major strength of this study is the detailed, self-reported, reproductive history available from a large ethnically and socio-economically diverse cohort becoming pregnant at high altitude. The prevalence of miscarriage is difficult to study in large populations, due to incomplete reporting and inconsistent terminology.37 Therefore, the contemporaneous recording of detailed reproductive histories from individual women to a limited group of trained medical professionals is an important feature of this data set. Although there is no way of independently verifying the reproductive histories given by the women in the data set, previous studies have shown that such information is likely to be highly reliable.37,38 The well-established and validated methodology16,39 used to determine the ancestry group in this particular population is also a major strength of the study. Moreover, the detailed co-variate set available and the robust modeling strategy to take account of different reproductive patterns in different ancestry groups also allow for a valid standardized comparison of miscarriage rates.

We use a large detailed data set collected contemporaneously in Bolivia between 1974 and 1985. Currently, high altitude populations in Bolivia may be substantively different in terms of socioeconomic status, nutrition, and healthcare availability. However, the inter-group comparisons presented here are likely to be robust to changing conditions, particularly in view of our ability to adjust for socio-economic confounders in our analysis. Although maternal BMI was not significantly different between ancestry groups, there was too much missing data to include this important variable in the analysis of reproductive success. A further limitation is that it is assumed that the same male partner is the biological father of all the pregnancies experienced by each woman in the study timeframe. This is likely to be the case for the majority of women; however, it is not possible to identify women who had pregnancies with more than one partner within the available data. It is possible that there are inter-group socioeconomic differences that could impact access or use of contraceptives; however, independent reports suggest that contraceptives were in general rarely used in Bolivia in the 1980s.40,41 It is also possible that some miscarriages were not identified or reported to the doctors due to the lack of knowledge or stigma. However, there is no reason to believe that this would have varied between ancestry groups.

In summary, the data presented indicate that ancestry is an important determinant of reproductive success at high altitude. Andean ancestry confers protection on reproductive success at high altitude. As populations at high altitude expand with global population increases, these findings are likely to become significant for a wider variety of women. With financial pressures, growing population, environmental adaptation, and improved transport links all promoting an increase in the global number of high-altitude emigrants, increased genetic admixture in high altitude resident populations can be anticipated. Further understanding of the mechanisms underlying adaptation to early pregnancy at high altitude is valuable, not only in improving reproductive success for the growing number of pregnancies occurring above 3500 m, but also in further understanding of the mechanisms of miscarriage.

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CONFLICT OF INTEREST
The authors state there are no conflicts of interest.
AUTHOR CONTRIBUTIONS
R. Soria and D. Giussani collected the data. I. Grant analyzed the data. I. Grant, C. Aiken, D. Giussani, C. Julian, E. Vargas, and L. Moore wrote the paper.

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