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## Birth Weight of Infants of Mothers With Aggressive Periodontitis

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### Abstract

**Background**—It was hypothesized that if periodontal infections predispose low birth weights and premature birth, then such outcomes should be apparent when the mother has aggressive periodontitis (AgP).

**Methods**—Birth weight data were collected by questionnaire from females with AgP, their periodontally healthy siblings, and unrelated periodontally healthy women. Both prospective and retrospective birth outcome data were used. Because many of the periodontal evaluations were performed after the births, there were incomplete data regarding most of the risk factors for low birth weight. We determined associations between mothers' periodontal diagnoses and clinical variables and the reported birth weights.

**Results**—There were no significant differences in mean birth weights of babies born to control subjects or AgP patients. This was true whether all the births were considered or only those reported <1 or 2 years before periodontal examination. For periodontally healthy controls, 13.2% of babies born to siblings of AgP patients and 12.8% of babies born to unrelated mothers weighed <2,500 g, whereas 9.9% of those born to mothers with generalized AgP and 10.3% of those born to mothers with localized AgP weighed <2,500 g.

**Conclusions**—Because of the relative rarity of AgP in the population, and attendant difficulties in performing a prospective study of its association with pregnancy outcomes, we used a compromised approach using prospective data as well as weaker retrospective data assuming that disease onset was likely before the births. Our results, within the limitations of this approach, indicate no evidence that AgP in the mother predisposes low birth weights. AgP has many unique biologic characteristics that differentiate it from chronic forms of periodontal disease, and the possible lack of its association with birth weight may be another such characteristic.

### Keywords

Aggressive periodontitis; infant, low birth weight; pregnancy; preterm birth

Many recent studies have demonstrated significant associations between periodontal disease and adverse pregnancy outcomes.<sup>1,2</sup> A variety of measures of periodontal infection, including clinical measures of periodontal probing depth (PD), progression of periodontal disease during pregnancy,<sup>3</sup> immune responsiveness or lack thereof to periodontal microorganisms,<sup>4,5</sup> and specific bacterial colonization,<sup>4-7</sup> have been shown to be associated with low birth weight, premature birth, preeclampsia, and even fetal death. It has been hypothesized that systemic inflammation, attributable to periodontal infection and bacterial colonization in the absence of adequate maternal antibody responses to specific periodontal pathogens, might contribute to such adverse outcomes. Notably, other studies have failed to reproduce the associations between periodontal diseases and pregnancy outcomes.<sup>8-13</sup> Furthermore, although some studies<sup>14,15</sup> have shown that treatment of periodontal disease during pregnancy is of benefit to birth outcomes,<sup>16</sup> others have failed to show such an effect.<sup>17-19</sup>

Aggressive periodontitis (AgP), a disease with clinical onset typically in teenagers and young adults, is characterized by rapid loss of periodontal supporting tissues. It occurs in two distinct clinical patterns, including a localized form affecting first molars and incisors primarily and a generalized form that may affect all teeth.<sup>20</sup> The prevalence of AgP in teenagers in the United States has been estimated to be between 0.1% and 2% depending on the clinical subform of the disease, race, and sex of the subject population.<sup>21</sup> Thus, AgP, and particularly generalized aggressive periodontitis (GAgP), is a relatively rare disease.

The relative rarity of AgP mitigates against designing a practical prospective study of the impact of this severe form of periodontitis on pregnancy outcomes. Because the typical age of onset of AgP indicates a reasonably high likelihood that the presence of disease would co-occur with pregnancy, we thought it reasonable to perform an analysis using both prospective and retrospective birth outcome data in AgP based on information collected from mothers with this disease as well as their periodontally healthy (NP) female siblings and unrelated control NP subjects.

## MATERIALS AND METHODS

### Clinical Methods

This study was approved by the office of Research Subjects Protection for the Conduct of Human Research of Virginia Commonwealth University, Richmond, Virginia. All participants provided written informed consent prior to their participation in this study. This study was initially performed during a long-term series of studies<sup>22-25</sup> of clinical, genetic, and biologic aspects of AgP, which included a family study of these diseases. Thus, participants in the study included patients with AgP, their NP siblings, and unrelated NP subjects. Subjects were enrolled and examined from 1976 to 2010 at the Virginia Commonwealth University Clinical Research Center for Periodontal Disease. A total of 135 localized aggressive periodontitis (LAgP) subjects, 147 GAgP subjects, and 170 NP siblings of AgP subjects were identified during this time frame. Data collection for determination of birth outcomes for these subjects began in 1994. Periodontal examinations were performed at the time of initial examination. Subsequent to, or at the time of, initial or follow-up periodontal examination, 85 LAgP subjects, 84 GAgP subjects, and 125 NP siblings

completed questionnaires that asked questions about socioeconomic status and the birth weight and length of pregnancy for each of their children, if any. The number of subjects completing the questionnaire who provided information about their children is shown in Table 1.

The mothers provided a comprehensive health history and received a complete periodontal examination. Data on smoking history and racial category were determined by self-report. All subjects were systemically healthy as determined by history. The periodontal examination included PD, attachment loss (AL), plaque index (PI),<sup>26</sup> gingival index (GI),<sup>27</sup> and bleeding on probing (BOP).<sup>28</sup> Measurements of PD and AL were recorded to the nearest 1 mm with measures between 1 mm probe markings rounded down to the nearest millimeter. Measurements were performed at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual).

The definitions of AgP for the subjects in this report conform to current diagnostic guidelines for these diseases<sup>29</sup> with the additional restriction that all cases of GAgP conform to previous publications<sup>25</sup> from our group in which the criterion of “early onset” of disease was invoked. The diagnostic groupings were defined as follows: 1) NP subjects with no evidence of AL other than facial recession and no periodontal pockets >3 mm. 2) GAgP subjects had a history of disease onset <35 years of age and presented with 8 teeth with 5 mm AL at interproximal sites; 3 of the affected teeth were not first molars and incisors. 3) LAgP subjects had a history of disease onset <30 years of age and presented with 2 teeth with 4 mm AL (one of which was a first molar) and no >2 additional teeth with AL that were not first molars or incisors.

The age of onset of AL was routinely verified through dental records and radiographs throughout the course of the studies<sup>22–25</sup> from which this population was drawn. Furthermore, we routinely recalled and reexamined as many of these subjects as was possible to verify the diagnosis of AgP and assess progressive disease, and administered the survey form to assess birth outcomes during these follow-up examinations. The cases where female siblings of subjects displayed AL but could not be determined by follow-up examinations to have AgP were not included in the analyses.

## Statistical Analyses

Examination of the racial composition of the subjects completing the birth outcomes questionnaire revealed that 98.2% were either black or white, so data analyses were restricted to these two racial groups. Data were analyzed by analysis of variance. The model used for the analysis was a mixed model with a random error term for the mother. Adding the random error term allows the model to take into account correlation of observations among babies of the same mother. The latter was necessary because there were multiple births for many of the mothers. The response variable was birth weight (in grams). The fixed terms modeled in the analyses were as follows: 1) race; 2) periodontitis group (GAgP, LAgP, and two non-periodontitis control groups); 3) interaction between patient group and race; 4) smoker status (current, never, former); 5) GI, PI, PD, and AL; 6) months between examination and birth; and 7) mother’s age at birth. The previous model was done using statistical software.<sup>‡</sup> When we evaluated the frequency of low-birth-weight infants, a similar

analysis was done with generalized estimating equation (GEE) methods for the binary outcome of <2,500 or greater. In the GEE models (done using a function in the statistical software<sup>‡</sup>), the terms in the model were restricted to race, smoking, mother's age at birth, and participant group to allow convergence.

## RESULTS

Data regarding birth weights and the length of pregnancy were collected by survey from 80 females with GAgP, 50 females with LAgP, and 135 NP female control subjects who were either siblings of the AgP subjects or unrelated. Table 1 illustrates the mean values of the periodontal variables for the mothers in the four groups. The data are characteristic of the groups.

Demographic variables describing the subjects are shown in Table 2. The time between periodontal examination and the child's birth was less for the AgP groups. The distribution of the time between the periodontal examination and the birth of the child is shown in Figure 1. For all births, 32% of the periodontal examinations were performed either before birth or within 2 years after birth.

The mean birth weights for the four groups are shown in Table 3. Despite significant clinical differences between the AgP groups and the NP subjects, there were no significant differences in the birth weights. To ensure that the relative birth weights were not biased by the amount of time that had elapsed since the births and that periodontal clinical data collected close to the time of birth was not different from data collected several years after birth, we calculated mean birth weights for subsets of the groups according to the interval between birth and periodontal assessment. Mean birth weights for the diagnostic groups were equivalent regardless of the time between birth and periodontal examination (Table 3). This was further substantiated by analysis of covariance, where the number of months between birth and periodontal examination and whether the examination was performed before or after the birth, was used as a covariate in an analysis of the effects of periodontal diagnosis on birth weight ( $P = 0.9$ ).

We then determined the frequencies of reported low birth weight (defined as <2,500 g) within the diagnostic categories (Table 4). There were no statistically significant differences between groups for preterm birth. This was true whether we considered all the births or only those reported <1 or 2 years before periodontal examination. The percentage of low birth weight ranged from 9.9% to 17.3% ( $P = 0.91$ ). The lowest proportion of preterm births occurred in the GAgP group.

Because of the frequently reported differences in adverse pregnancy outcomes between white and black individuals in the United States, we further examined birth weight within these racial groups. As seen in Table 5, birth weight was significantly influenced by race ( $P = 0.001$ ) but not by periodontal condition, smoking habits, mother's age, or the interval between periodontal examination and birth. In addition, because our participant cohort

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<sup>‡</sup>JMP software, SAS, Cary, NC.

<sup>§</sup>PROC GENMOD function, SAS.

contained a significant number of young subjects who could be at increased risk for preterm low birth weight, we compared birth weights of babies born to teenagers (< 19 years) to those born to mothers >19 years old. Teenage subjects had significantly smaller babies ( $P = 0.009$ ) than non-teenagers. However, analyses of birth weights between diagnostic groups that included teenage status as a covariate failed to alter the observation that no difference in birth weights between diagnostic groups could be observed ( $P = 0.89$ ).

Finally, we examined the reported birth outcomes in the most severely affected GAgP subjects compared to the NP subjects by restricting the AgP subjects to those with >50% of their teeth with >5 mm AL. No differences were noted in birth weight ( $P = 0.47$ ) among the GAgP subjects and the two NP groups.

## DISCUSSION

The data indicate that there is no significant influence of AgP on birth outcomes. In some respects, this result is surprising given the recent literature<sup>1,2</sup> indicating that periodontal disease is associated with, and possibly a risk factor for, preterm-birth and low birth weight. AgP is a relatively severe form of periodontal disease that is most apparent in teenagers and young adults. This engendered our hypothesis that, because periodontal disease is considered to be a likely risk factor for adverse pregnancy outcome, we would readily see differences in birth outcome among patients with early-onset severe disease and healthy individuals. In fact, our expectation was that this group would experience more severe adverse pregnancy outcomes than any other periodontal diagnostic group, which was not the case.

Numerous studies have been performed that demonstrate the validity and accuracy of maternal recall of their infants' birth weights.<sup>30–35</sup> These studies uniformly show that maternal recall of their infants' birth weight generally has a correlation with information from birth certificates of >0.9, this remains accurate even 30 years after the child's birth, and varies only slightly with mother's educational level. In a study of >46,000 females in Tennessee in which reported birth weights were compared to birth records, only 1.1% of births could be misclassified as either low birth weight or preterm.<sup>32</sup> Thus, it is highly likely that the birth weights reported in this study were accurately reported with a small and acceptable level of error.

When there is a lack of a statistically significant difference between groups, this result can be real or attributable to a lack of statistical power. Because this report describes a cohort of subjects identified during a family study of genetic risk, we did not develop a formal power analysis before creating this report. However, we did perform a power analysis after the completion of data collection for this study. Because there were multiple children per mother and  $\approx 50\%$  of the variance was explained by a random error term, we based this power analysis on a sample size of the 135 mothers in the two periodontally healthy groups and the 80 GAgP mothers. This approach provided a conservative power estimate. At 80% power, we could have found a difference of 238 g between the children of the healthy mothers and the children of the AgP mothers. We did not do a power analysis for the prevalence of low-birth-weight babies, but the prevalence of low-birth-weight babies in the

AgP group was 9.9%, which was  $\approx 3\%$  lower than the NP mothers. The number of mothers in our study is similar to that in a report by Offenbacher et al.<sup>36</sup> in which the authors were investigating the relationships between periodontal disease and birth outcomes. In that report, the authors were able to find statistically significant differences in both birth weight and the prevalence of low-birth-weight babies between NP mothers ( $n = 201$ ) and mothers with moderate-to-severe chronic periodontal disease ( $n = 45$ ). Thus, there appears to be adequate statistical power in the current study to find meaningful differences between the groups.

Although there are obvious inherent weaknesses associated with the design of a study in which retrospective data are used and in which many of the periodontal assessments are performed several years after pregnancy, this approach is more feasible for examination of birth outcomes in AgP than a prospective study. Aggressive forms of periodontitis are relatively rare conditions,<sup>21</sup> and a prospective study with adequate numbers of subjects would be impractical. The retrospective approach takes advantage of the fact that AgP, and particularly GAgP, is known to have onset and progression during the late teenage years and early 20s, when females would be most likely to be having children. The mean maternal age for birth of the children reported on in this study is 23.5 to 26 years, depending on the group, and it is reasonable to assume that the periodontal condition of most of the AgP subjects had developed by that time and that disease was present at the time of birth. Additionally, it is obvious that the control subjects did not have periodontitis at the time of the birth of their children. Most importantly, sufficient numbers of subjects were examined within 1 or 2 years of the births of their children to ensure that the relationships between periodontal status and birth weights reported herein are likely to be valid.

We included two NP control groups in this study. It is established that AgP is a familial condition that likely has a significant underlying genetic etiology.<sup>23,37,38</sup> Thus, we considered it imperative to include an NP group of mothers who were first-degree relatives of the subjects with AgP. In this way, we would be able to differentiate between familial effects on birth outcomes that could be specific to AgP families and comparative effects to non-family NP subjects. However, there were no apparent differences in birth outcomes among the groups.

Data regarding periodontal treatment was self-reported by the AgP subjects on the same questionnaire used for reports of pregnancy outcomes. However, we do not have systematic data regarding the extent, nature, or outcome of the therapy. We performed an analysis of reported birth weight as a function of whether the individual reported receiving therapy. The results indicate that there was no difference in birth weight in the diagnostic for subjects receiving or not receiving therapy ( $P = 0.46$ ).

The clinical periodontal “exposure” that is required to influence pregnancy outcomes is not entirely clear. Many of the studies that demonstrate associations between periodontal disease and preterm birth or low birth weight note that measures of PD, AL, or GI and BOP are the important clinical variables that impact pregnancy.<sup>3,39–42</sup> Examination of these variables in our groups demonstrates significantly greater PI, GI, BOP, and PD measures in the GAgP group than in the other clinic group (all  $P < 0.0001$  compared to all other groups) without

impact on pregnancy outcome. We also considered the possibility that only the most severely affected GAgP subjects might demonstrate significant effects of their periodontal condition on birth outcomes, so we compared the pregnancy outcomes for the most severely affected mothers with controls. Again, there was no significant effect. It is important to note, however, that these variables were measured in some of the mothers several years after the reported births (Table 1) and may not reflect the clinical measures that would have been observed during pregnancy.

We were concerned that the population studied herein might not be reflective of the population in general with respect to pregnancy outcomes, so we obtained data reporting the mean birth weights in the Richmond, Virginia area by race for the years 1997 to 2007. These data indicated that mean birth weights were very similar in the population in general (blacks,  $3,047.0 \pm 661.2$  g; whites,  $3,338.5 \pm 583.9$  g) to those in our subjects (Tables 3 and 5). Thus, it is unlikely that the population studied is unique with respect to pregnancy outcomes.

There are ample data in the literature indicating that AgP subjects demonstrate unique biologic characteristics with respect to inflammatory and immunologic responsiveness and genetic susceptibility.<sup>25,43–46</sup> In this regard, an explanation for our failure to detect an influence of AgP on pregnancy outcomes could relate to fundamental biologic differences between AgP and gingivitis or chronic periodontitis. For example, inflammation is a hallmark of preterm labor,<sup>47,48</sup> and aberrations in the systemic inflammatory response, such as impaired neutrophil function or alterations in T-cell regulatory profiles that control inflammatory responses, may provide a more favorable environment for pregnancy in AgP subjects. Additionally, we and others have noted differences in the microbial flora of AgP compared to chronic periodontitis and gingivitis<sup>49</sup> that could account for variable pathogenic potential with respect to effects on pregnancy outcomes.

## CONCLUSIONS

The data from this study fail to demonstrate an impact of AgP on birth weight. Although a study that incorporates a significant amount of retrospective data has some clear weaknesses compared to an entirely prospective study, the typical age of onset and progression of AgP, and especially GAgP, would strengthen the interpretation of the result because it is likely that the majority of the AgP mothers were affected by the disease at the time of their children's births.

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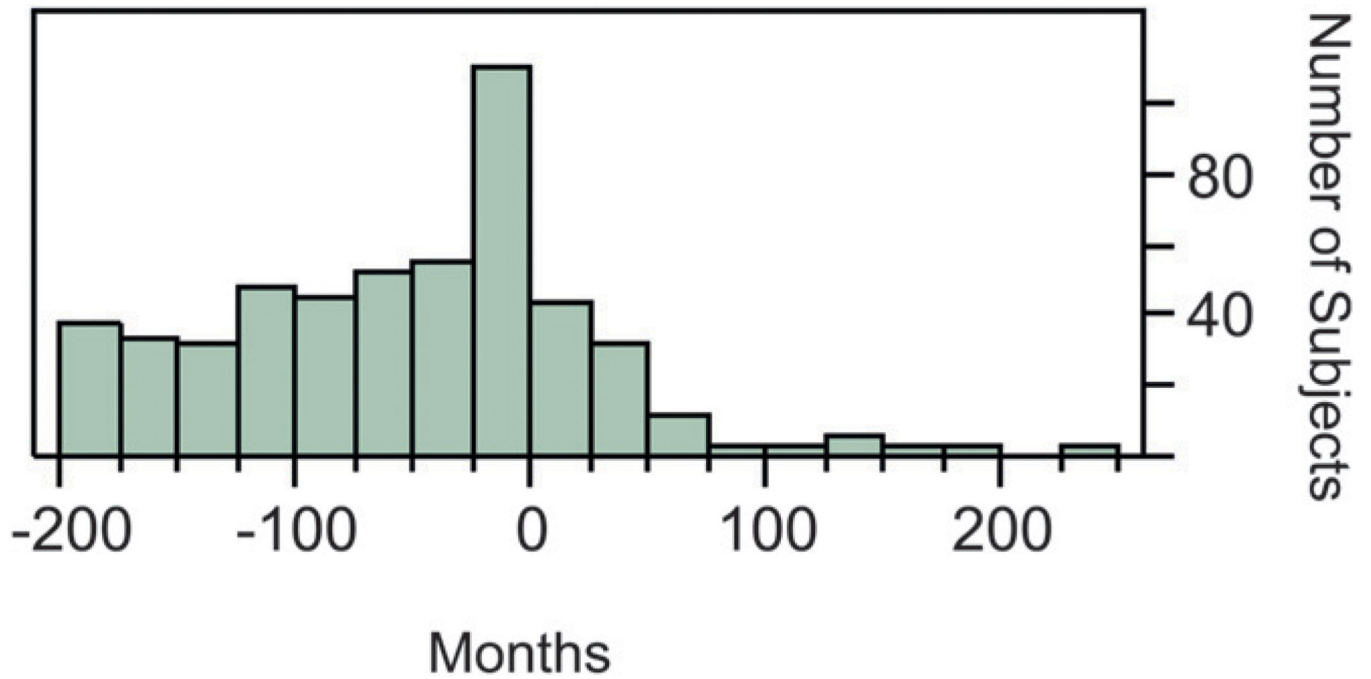
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**Figure 1.** Months between periodontal examination and the birth of the child. Negative numbers indicate that the birth preceded the periodontal examination.

**Table 1**

Periodontal Measures in Subject Groups

Diagnosis	n	PI		GI		PD		AL		2%		5%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
NP, unrelated	90	0.45	0.36	0.67	0.31	2.06	0.26	0.18	0.22	3.4	5.8	0	0
NP, siblings	45	0.77	0.46	0.95	0.40	2.04	0.31	0.14	0.16	3.4	4.4	0	0
LAgP	50	0.67	0.37	0.95	0.40	2.40	0.38	0.61	0.44	15.2	11.1	2.9	3.4
GAgP	80	1.22	0.53	1.46	0.50	3.76	1.01	2.81	1.55	61.4	22.0	23.2	20.3

2% = percentage of sites with < 2 mm AL; 5% = percentage of sites with > 5 mm AL.

**Table 2**

## Demographic Variables in Subject Groups

Variable	GAgP	LAgP	NP (Siblings)	NP (Unrelated)
Mean age at diagnosis $\pm$ SD	16.4 $\pm$ 2.9	15.5 $\pm$ 1.9	18.3 $\pm$ 5.4	20.0 $\pm$ 7.2
Mean age at child's birth $\pm$ SD	24.2 $\pm$ 5.5	25.0 $\pm$ 5.6	23.5 $\pm$ 5.4	26.0 $\pm$ 5.6
Race (% black)	72	82	68	52
Smoking history (% for current, former, never)	55, 1, 44	24, 2, 75	40, 8, 52	29, 1, 71
Family income (% for < \$25,000, \$25,000 to \$40,000)	82, 13	71, 24	65, 24	59, 25
Periodontal therapy received (%)	39.5%	64.9%	N/A	N/A
Months pregnant $\pm$ SD	8.9 $\pm$ 0.3	8.9 $\pm$ 0.5	8.8 $\pm$ 0.7	8.7 $\pm$ 1.1

N/A = not applicable.

**Table 3**

Birth Weight in Groups Examined at Different Time Intervals in Relation to Time of Birth

Timing of Mother's Periodontal Examination Relative to Child's Birth	Birth Weight (Grams)*		
	n	Mean	SD
All examinations			
NP, unrelated	180	3,229.6	845.0
NP, siblings	106	3,163.9	715.4
LAgP	97	3,252.9	636.7
GAgP	223	3,244.6	581.9
Examinations before birth only			
NP, unrelated	12	3,401.9	584.8
NP, siblings	19	3,166.2	716.0
LAgP	23	3,347.7	626.0
GAgP	39	3,179.5	621.6
Examinations before birth and within 1 year after birth			
NP, unrelated	24	3,210.6	876.2
NP, siblings	32	3,189.3	603.7
LAgP	54	3,229.1	783.8
GAgP	53	3,191.7	637.5
Examinations before birth and within 2 years after birth			
NP, unrelated	33	3,258.5	823.1
NP, siblings	37	3,193.5	612.2
LAgP	60	3,263.5	752.1
GAgP	65	3,234.0	635.5

\* No statistical differences were noted among groups.

**Table 4**

Frequency of Low Birth Weight (&lt;2,500 g) in Subject Groups

<b>Timing of Mother's Periodontal Evaluation Relative to Child's Birth</b>	<b>n</b>	<b>n for Low Birth Weight*</b>	<b>% of Low Birth Weight</b>
All examinations			
NP, unrelated	180	23	12.8
NP, siblings	106	14	13.2
LAgP	97	10	10.3
GAgP	223	22	9.9
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Examinations before birth and within 1 year after birth			
LAgP	52	9	17.3
GAgP	53	7	13.2
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Examinations before birth and within 2 years after birth			
LAgP	60	9	15.0
GAgP	65	8	12.3

\* No statistical differences were noted among groups.

**Table 5**

## Birth Weight in Subject Groups by Race

Race	n	Birth Weight (g)*	
		Mean	SD
NP, unrelated	171	3,317	656
Black	91	3,183	655
White	80	3,468	627
NP, related	103	3,163	612
Black	72	3,109	657
White	31	3,291	477
LAgP	95	3,250	642
Black	80	3,218	650
White	15	3,421	590
GAgP	219	3,213	577
Black	159	3,079	506
White	60	3,573	604

\* No significant differences were noted for birth weight between diagnostic categories ( $P > 0.9$ ). Black subjects had significantly lower birth weight ( $< 0.001$ ) than white subjects. Analyses were corrected for age of the mother, time between birth, and dental examination and smoking.