American Journal of Obstetrics and Gynecology (2005) **192**, 882–6

American Journal of OBSTETRICS and GYNECOLOGY
www.ajog.org

The Preterm Prediction study: Association between maternal body mass index and spontaneous and indicated preterm birth

Israel Hendler, MD,* Robert L. Goldenberg, MD, Brian M. Mercer, MD, Jay D. Iams, MD, Paul J. Meis, MD, Atef H. Moawad, MD, Cora A. MacPherson, PhD, Steve N. Caritis, MD, Menachem Miodovnik, MD, Kate M. Menard, MD, Gary R. Thurnau, MD, Yoram Sorokin, MD

National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network, National Institutes of Health, Bethesda, Md

Received for publication June 18, 2004; revised August 31, 2004; accepted September 15, 2004

KEY WORDS
Maternal obesity
Spontaneous preterm birth
Body mass index

Objective: The purpose of this study was to evaluate the relationship between prepregnancy maternal body mass index and spontaneous preterm birth and indicated preterm birth.
Study design: This was a secondary analysis of the Maternal-Fetal Medicine Units Network, Preterm Prediction study. Patients were classified into categories that were based on their body mass index. Rates of indicated and spontaneous preterm birth were compared.
Results: Five hundred ninety-seven (20.5%) of 2910 women were obese. Obese women had fewer spontaneous preterm births at <37 weeks of gestation (6.2% vs 11.2%; $P < .001$) and at <34 weeks of gestation (1.5% vs 3.5%; $P = .012$). Women with a body mass index of <19 kg/m^2 had 16.6% spontaneous preterm birth, with a body mass index of 19 to 24.9 kg/m^2 had 11.3% spontaneous preterm birth, with a body mass index of 25 to 29.9 kg/m^2 had 8.1% spontaneous preterm birth, with a body mass index of 30 to 34.9 kg/m^2 had 7.1% spontaneous preterm birth, and with a body mass index of ≥ 35 kg/m^2 had 5.2% spontaneous preterm birth ($P < .0001$). Indicated delivery was responsible for an increasing proportion of preterm births with increasing body mass index ($P = .001$). Obese women had lower rates of cervical length <25 mm (5% vs 8%; $P = .012$). Multivariable regression analysis confirmed a lower rate of spontaneous preterm birth in obese gravid women (odds ratio, 0.57; 95% CI, 0.39-0.83; $P = .003$).
Conclusion: Obesity before pregnancy is associated with a lower rate of spontaneous preterm birth.

Supported by grants from the National Institute of Child Health and Human Development: HD27917, HD27869, D27915, HD27860, HD27861, HD21410, HD27889, HD21410, HD 27905, HD27889, HD21414, HD27889, HD19897 and HD36801.
Presented at the Society for Gynecologic Investigation annual meeting, March 22-27, 2004, Houston, Tex.
* Reprint requests: Israel Hendler MD, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Hutzel Hospital-Wayne State University, 3990 John R Rd, Detroit, MI 48201.
E-mail: ihendler@med.wayne.edu

0002-9378/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajog.2004.09.021

Table I Characteristics and pregnancy outcome in obese and nonobese women

Patients characteristic	Obese (n = 597)	Nonobese (n = 2313)	*P* value
BMI (kg/m^2)*	36.2 ± 5.3	22.7 ± 3.5	< .0001
Maternal age (y)*	25.7 ± 5.6	23.3 ± 5.4	< .0001
Gravidity (n)*	3.0 ± 1.8	2.6 ± 1.6	< .0001
Nulliparity (%)	33	44	< .0001
Education (y)*	12.1 ± 1.7	11.8 ± 2.0	< .0001
Married (%)	33	27	.005
Previous SPB (%)	10	13	.019
Black race (%)	65	62	.15
Smoking (%)	29	31	.31
Family income <$800/mo (%)	64	61	.15
Gestation at delivery (wk)*	38.6 ± 2.5	38.3 ± 2.6	.005
Cesarean delivery (%)	29	15	< .0001
Birth weight (g)*	3287 ± 660	3114 ± 633	< .0001
Birth weight >4000 g (%)	10	5	< .0001

* Data are given as mean ± SD.

Obesity is defined by the National Institutes of Health as a body mass index (BMI) of ≥30 kg/m^2.[1] The prevalence of obesity among adults in the United States has increased from 12% in 1991 to 20.9% in 2001.[2] Obesity in nonpregnant women is a known risk factor for many disorders, including diabetes mellitus, atherosclerosis, and certain malignancies, and it is the second leading cause of preventable death in the United States.[3,4] Previous studies have reported the association between maternal obesity and many adverse pregnancy outcomes, which include fetal anomalies, miscarriages, preeclampsia, gestational diabetes mellitus, cesarean deliveries, shoulder dystocia, and intrauterine fetal demise.[5-14] However, evidence regarding the association of maternal obesity and spontaneous preterm birth (SPB) is conflicting. Although some studies suggest that obesity does not influence the rate of preterm birth at <37 weeks of gestation,[6-8,13] other studies have found reduced rates of preterm birth in obese and morbidly obese patients.[9,11,12,14] Finally, other studies have reported increased preterm birth in obese gravidas.[10] Of note, in these retrospective studies, the main objective was to assess the adverse effects of obesity on pregnancy; preterm birth was one of many variables that were studied; the type of preterm birth (ie, after spontaneous preterm labor, preterm premature rupture of membranes, or indicated labor) was not distinguished, and confounding variables that were associated with preterm birth were not addressed.

At the other end of the spectrum, low maternal weight has been associated repeatedly with an increased risk of SPB.[15-20] In a previous analysis from the Preterm Prediction Study of the Maternal-Fetal Medicine Units Network, we evaluated clinical risk factors for preterm birth and found a significantly increased risk of SPB with maternal BMI at <19.8 kg/m^2.[19] The purpose of this analysis was to further evaluate the relationship between maternal BMI and the rate of spontaneous and indicated preterm birth, after controlling for potentially confounding factors, in a prospectively evaluated cohort of women.

Material and methods

This was a secondary analysis of the prospective observational Preterm Prediction Study performed by the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. The primary study was conducted in 10 medical centers from 1992 to 1994. The overall study population and methods for this study has been described previously and will be briefly reviewed.[21] Institutional Review Board approval was obtained at each of the 10 centers that participated in the original investigation. Each study participant provided informed consent. Exclusion criteria included multifetal gestation, prenatally detected major fetal anomalies, a history of cervical cerclage in the current pregnancy and placenta previa. Gestational age was based on the last menstrual period, if the last menstrual period and the earliest ultrasound evaluation agreed within 10 days. If not, the earliest ultrasound evaluation was used to define gestational age. The initial study visit occurred at 23 to 24 weeks of gestation, with 3 additional visits scheduled at 2-week intervals until 31 weeks of gestation. Extensive demographic and outcome data were collected. Samples of maternal serum and cervical fluid, which included Gram stain for diagnosis of bacterial vaginosis, were collected at the initial (23-24 weeks of gestation) and the third visit (27-28 weeks of gestation).

We performed a secondary analysis on all patients for whom maternal height and pre-pregnancy weight were available. Prepregnancy maternal BMI was calculated

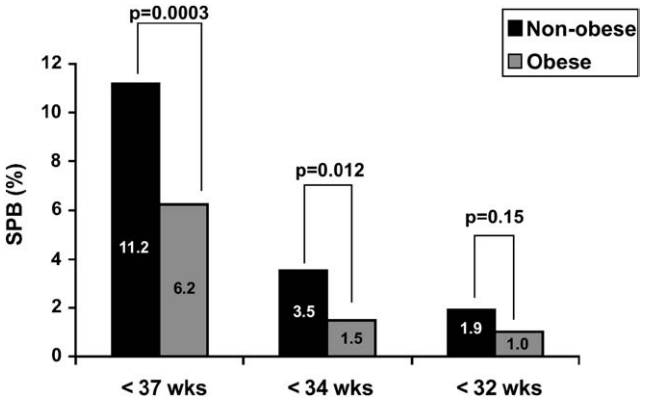

Figure 1 The percent of spontaneous preterm birth (*SPB*) at <37, at <34, and at <32 weeks of gestation in nonobese and obese patients.

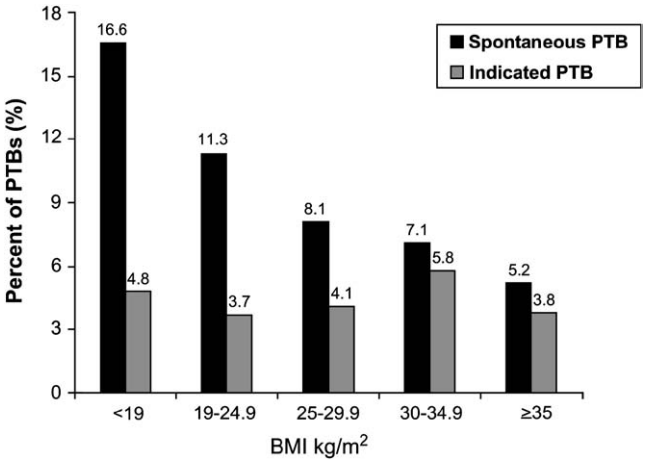

Figure 2 The percent of spontaneous (*SPB*) and indicated preterm births (*PTB*) at <37 weeks of gestation in various BMI groups.

for each patient (weight in kilograms/height in meters^2). For some of the analyses, patients were classified as nonobese (BMI, <30 kg/m^2) or obese (BMI, ≥30 kg/m^2), for other analyses, women were classified into groups according to the National Institutes of Health guidelines,[1] underweight (BMI, <19 kg/m^2), normal weight (BMI, 19-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), class I obesity (BMI, 30-34.9 kg/m^2), and class II or morbid obesity (BMI, ≥35 kg/m^2). Our primary outcome was SPB because of premature rupture of membranes or spontaneous labor before 37 weeks of gestation. Other outcomes included SPB at <34 and <32 weeks and the rate of indicated preterm birth.

Statistical analyses were performed with the SAS software (version 8.2; SAS Institute Inc, Cary, NC). Categoric variables were compared with the use of the chi-squared and Fisher's exact tests. The Mantel-Haenszel chi-squared test was used to test for trends across BMI categories. Multivariable logistic regression was used to assess the relationship between SPB and maternal BMI, while being controlled for potential confounders (age, race, previous SPB, bacterial vaginosis, fetal fibronectin, and cervical length [CL]).

Results

A total of 2910 of the originally enrolled 2929 patients met eligibility requirements and were included in this analysis. There were 597 obese women (BMI, ≥30 kg/m^2; 20.5%). Obese women were older than nonobese women, were more likely to be multiparous, had more years of education, were married more often, and were less likely to have had a previous spontaneous preterm delivery (10% vs 13%; $P = .019$) than nonobese women (Table I). However, there were no differences in the rate of smoking, race, or family income between groups. Obese women had larger infants (3287 ± 660 g vs. 3114 ± 633 g; $P < .0001$), delivered at a more advanced gestational age (38.6 ± 2.5 weeks vs 38.3 ± 2.6 weeks; $P = .005$), and had more frequent cesarean deliveries (29% vs 15%; $P < .0001$). Obese patients had significantly lower rates of SPB at <37 weeks of gestation (6.2% vs 11.2%; $P = .0003$), and at <34 weeks of gestation (1.5% vs 3.5%; $P = .012$; Figure 1). The odds ratio (OR; 95% CI) of an obese patient to have a SPB was approximately one-half that for a nonobese patient (<37 weeks of gestation: OR, 0.5; 95% CI, 0.4-0.7; <34 weeks of gestation: OR, 0.4; 95% CI, 0.2-0.8; <32 weeks of gestation: OR, 0.5, 95% CI, 0.2-1.3).

When the patients' BMIs were classified into groups according to the National Institutes of Health guidelines,[1] the risk of SPB at <37 weeks of gestation progressively decreased with increasing BMI: underweight, 16.6%; normal weight, 11.3%; overweight, 8.1%; class I obesity, 7.1%; class II or morbid obesity, 5.2%; $P < .0001$; Figure 2).

The total rate of preterm deliveries, which included both spontaneous and indicated deliveries, was also lower in obese women (11.1% vs 15.3%; $P = .009$). The frequency of indicated preterm birth was comparable in obese and nonobese patients (4.9% vs 4.0%), but indicated preterm birth accounted for a higher percentage of preterm birth in the obese than nonobese patient (44% vs 24%; $P = .003$). Figure 2 shows the relative proportions of indicated preterm birth and SPB for each BMI group. In obese patients, 18 of 29 indicated preterm deliveries (62%) were due to maternal preeclampsia, compared with 33 of 92 indicated preterm deliveries (36%) for the nonobese women ($P = .013$). Among women who were delivered at <37 weeks of gestation, we found indicated preterm birth to be responsible for an increasing proportion of preterm births with increasing maternal BMI ($P = .001$).

Obese women had a longer CL compared with nonobese women, (36.5 ± 8.4 mm vs 34.9 ± 8.1 mm;

$P < .0001$; Table II). Obese women had lower rates of CL < 30 mm (16% vs 21%; $P = .02$) and CL <25 mm (5% vs 8%; $P = .012$). However, fetal fibronectin positivity and bacterial vaginosis were comparable among obese and nonobese gravidas.

Multivariable logistic regression analysis was performed to adjust for confounding variables that are known to be associated with SPB: maternal age, parity, education, history of SPB, black race, bacterial vaginosis, fetal fibronectin positivity, and CL at 23 to 24 weeks of gestation. Obesity was associated significantly with decreased SPB at <37 weeks of gestation (OR, 0.57; 95% CI, 0.39-0.83; $P = .003$). The results were similar, but not significant, for SPB at <34 weeks of gestation (OR, 0.58; 95% CI, 0.28-1.21; $P = .15$). When BMI was included in the model as a continuous variable, the adjusted odds ratio for SPB at <37 weeks of gestation declined by 21% for each 5-unit increase in maternal BMI ($P < .0001$).

Table II Tests predictive of SPB at 24 weeks of gestation in obese and nonobese women

Clinical characteristic (visit 1)	Obese (n = 595)	Nonobese (n = 2301)	*P* value
CL (mm)*	36.5 ± 8.4	34.9 ± 8.1	< .0001
CL <30 mm (%)	16.5	21.0	.015
CL <25 mm (%)	5.2	8.3	.012
CL <20 mm (%)	2.7	3.2	.51
Fetal fibronectin positive (%)	3.4	4.2	.37
Bacterial vaginosis positive (%)	23.5	23.1	.84

* Data are given as mean ± SD.

Comment

BMI, which is derived from the weight and height measurements, is one of the best markers of nutritional status and is used to classify populations from thin to obese. In this study, we evaluated the entire range of prepregnancy BMIs and compared them to the rates of indicated preterm births and SPBs. We found that prepregnancy obesity, defined as BMI ≥30 kg/m^2, was associated with fewer total preterm births and fewer SPBs. Maternal thinness on the other hand was associated with increased preterm birth and especially SPBs. A significantly high percentage of the preterm births of obese women were indicated, often in association with preeclampsia, compared with the preterm births of thin women. An additional finding is that obese women tended to have longer CLs than nonobese women.

In agreement with our results, Gross et al[11] found that obese patients (body weight >90 kg) had a 9.9% rate of preterm birth at <38 weeks of gestation compared with 19.9% for nonobese patients. Kumari[12] analyzed 488 morbidly obese patients (BMI, ≥40 kg/m^2) and found an OR of 0.1 (95% CI, 0.01-0.7) for preterm birth at <37 weeks of gestation. Sebire et al[9] found that obese gravidas (n = 287,213) had a reduced risk for preterm birth at <32 weeks of gestation (OR, 0.81; 95% CI, 0.69-0.95) but not at <37 weeks of gestation; Cnattingius et al[10] found an increased risk for SPB (n = 167,750) at ≤32 weeks of gestation in obese nulliparous patients (OR, 1.6; 95% CI, 1.1-1.3). Alternatively, Cedergren[13] found an increased risk for PTB (n = 805,275) at <37 and <32 weeks of gestation (4.5% and 0.6% for BMI <29 kg/m^2, compared with 5.4% and 0.8% for BMI 29.0-35 kg/m^2).

The disparity in results between different studies may be due to the use of population registries, to different definitions of spontaneous and indicated preterm birth, or to the different populations that are studied. Our analysis has the benefit of being based on prospectively collected data in a study that was aimed to determine risk factors for SPB, and the results are corrected for confounding variables that are associated with SPB.

Many studies have found an association between low maternal weight and an increased risk of SPB.[15-20] Ehrenberg et al[15] recently described a population of 15,196 patients in which low BMI (<19.8 kg/m^2) at conception and low BMI at the time of birth were associated with an increased risk for SPB. Using a multivariable analysis in a population of 17,000 patients, Wen et al[20] showed that a previous preterm delivery and very low maternal weight had the greatest association with preterm birth. Thus, because low maternal weight is associated with an increased rate of SPB, there may be a continuous inverse association between BMI and the risk for SPB.

Obese women had lower rates of CL of <30 mm (17% vs 21%; $P = .02$) and CL of <25 mm (5% vs 8%; $P = .012$). Similar results were found in Thai women, in whom the cervix was significantly longer in women with a BMI of >26 kg/m^2.[22] The longer CL may explain part of the reduced rate of SPB that is seen in obese women.

Preterm births that occur <30 weeks of gestation are more often associated with intra-amniotic inflammation and infection.[23,24] Maternal obesity is known to be associated with an increased production of systemic proinflammatory cytokines.[25] Thus, the reduced rate of spontaneous preterm labor in the obese population is not likely due to a reduced systemic inflammatory process, but whether an actual infectious process is involved is unknown. Some studies describe malnutrition as a factor in the cause of SPB. Decreased intake of calories, proteins, vitamins, and minerals, which often are associated with decreased BMI, may explain the higher rate of SPB in thin patients.[16] In obese women, the increased intake of various nutrients may be related to a reduced rate of SPB. However, by an unknown mechanism, obesity is associated with an increased risk

of preeclampsia; thus, the rate of indicated preterm births is increased in obese women.

In summary, we found a strong inverse association between prepregnancy BMI and SPB at <37 weeks of gestation. Further research is needed to investigate the different mechanisms that are responsible for spontaneous and indicated preterm birth in obese and nonobese women.

Acknowledgments

Participating institutions and staff members: University of Alabama, Birmingham: J.C. Hauth, A. Northen, R. Copper, C. Neely; Bowman Gray School of Medicine: E. Mueller-Heubach, M. Swain, A. Frye; University of Chicago: M. Lindheimer, P. Jones, M.E. Lewis-Brown; University of Cincinnati: T.A. Siddiqi, N. Elder, T. Coombs, J. VanHorn; George Washington University Biostatistics Center: E. Thom, R. Bain, A. Das, L. Leuchtenburg, M. Fischer; University of Pittsburgh Magee Women's Hospital: J.H. Harger, M. Cotroneo, C. Stallings; National Institutes of Child Health and Human Development: D. McNellis, S. Yaffe, C. Catz, M. Klebanoff; Ohio State University: M.B. Landon, F. Johnson, J. Schneider, C. Mueller; University of Oklahoma, Oklahoma City: J.C. Carey, A. Meier, E. Liles; Medical University of South Carolina: R.B. Newman, B.A. Collins, J.T. VanDorsten, F. LeBoeuf; Odell; University of Tennessee, Memphis: B. Sibai, R. Ramsey, J.L. Fricke; Wayne State University: S. Bottoms (deceased), M.P. Dombrowski, M. Treadwell, G.S. Norman; and University of Pittsburgh: J.M. Roberts, Steering Committee Chair.

References

1. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication No. 98-4083. Bethesda (MD): Department of Health and Human Services, National Institutes of Health; 1998.
2. Vastag B. Obesity is now on everyone's plate. JAMA 2004; 291:1186-8.
3. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors. JAMA 2003;289:76-9.
4. Manson JE, Bassuk SS. Obesity in the United States: a fresh look at its high toll. JAMA 2003;289:229-30.
5. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics 2003; 111:1152-8.
6. Jensen DM, Damm P, Sorensen B, Molsted-Pederson L, Westergaard JG, Oveson P, et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol 2003;189:239-44.
7. Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. Obstet Gynecol 2003;102:1022-7.
8. Castro LC, Avina RL. Maternal obesity and pregnancy outcomes. Curr Opin Obstet Gynecol 2002;14:601-6.
9. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Jaffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord 2001;25:1175-82.
10. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med 1998;338:147-52.
11. Gross T, Sokol RJ, King KC. Obesity in pregnancy: risks and outcome. Obstet Gynecol 1980;56:446-50.
12. Kumari AS. Pregnancy outcome in women with morbid obesity. Int J Gynaecol Obstet 2001;73:101-7.
13. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004;103:219-24.
14. Schieve LA, Cogswell ME, Scanlon KS, Perry G, Ferre C, Blackmore-Prince C, et al. Prepregnancy body mass index and pregnancy weight gain: associations with preterm delivery: the NMIHS Collaborative Study Group. Obstet Gynecol 2000; 96:194-200.
15. Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. Am J Obstet Gynecol 2003;189:1726-30.
16. Neggers Y, Goldenberg RL. Some thoughts on body mass index, micronutrient intakes and pregnancy outcome. J Nutr 2003; 133:1737S-40S.
17. Hickey CA, Cliver SP, McNeal SF, Goldenberg RL. Low pregravid body mass index as a risk factor for preterm birth: variation by ethnic group. Obstet Gynecol 1997;89:206-12.
18. Hickey CA, Cliver SP, McNeal SF, Hoffman HJ, Goldenberg RL. Prenatal weight gain patterns and spontaneous preterm birth among non-obese black and white women. Obstet Gynecol 1995;85:909-14.
19. Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, et al. The preterm prediction study: a clinical risk assessment system. Am J Obstet Gynecol 1996;174:1885-95.
20. Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP. Intrauterine growth retardation and preterm delivery: prenatal risk factors in an indigent population. Am J Obstet Gynecol 1990; 162:213-8.
21. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births: NICHD MFMU Network. Am J Public Health 1998;88:233-8.
22. Liabsuetrakul T, Suntharasaj T, Suwanrath C, Leetanaporn R, Rattanaprueksachart R, Tuntiseranee P. Serial translabial sonographic measurement of cervical dimensions between 24 and 34 weeks' gestation in pregnant Thai women. Ultrasound Obstet Gynecol 2002;20:168-73.
23. Iams JD. Prediction and early detection of preterm labor. Obstet Gynecol 2003;101:402-12.
24. Romero R, Ghezzi F, Yoon BH, Mazor M, Edwin SS, Berry SM. A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. Am J Obstet Gynecol 1998;179:186-93.
25. Ramsay JE, Crawford L, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. J Clin Endocrinol Metab 2002;87:4231-7.