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Acid base balance in pre-eclamptic, hypertensive and diabetic pregnancies. Maternal blood and amniotic fluid studies

Hossam E. Fadel, Gretajo Northrop, H. Robert Misenhimer, Rollie J. Harp

Dept. of Obstetrics and Gynecology and Internal Medicine, Rush Presbyterian—
St. Luke's Medical Center, Chicago, Il. 60612

Systems and Computer Services, Medical College of Georgia, Augusta, Georgia
30902

In previous communications we reported on the acid base balance in normal third trimester pregnancy [5, 6]. It was shown to represent a state of maximally compensated "sustained respiratory alkalosis" with no evidence of metabolic acidosis [6]. The amniotic fluid (AF) was found to be hypoxic and acidic by adult extracellular fluid standards [5]. The acid base balance in abnormal pregnancies have not been adequately investigated. There have been few reports describing some acid base parameters in cord, or fetal blood in few patients with hypertensive disorders [12, 13, 18] or diabetes mellitus [19]. There are even fewer studies of these parameters prior to onset of labor [3, 14, 16, 21]. There are no studies in which both the respiratory and metabolic components of the acid base balance, in blood, as well as AF, were investigated simultaneously.

The purpose of the present study was twofold. First, to determine if there are changes in the maternal acid base balance, in selected high risk pregnancies, that are superimposed on the changes of the normal pregnant state. Second, to determine the effects of intrauterine stress as exemplified by placental insufficiency (pre-eclampsia and hypertension) or metabolic disturbances (diabetes mellitus) on the acid base status of AF, which is thought to reflect that of the fetus [5].

1 Materials and methods

The subjects of this study were all third trimester pregnant women (30–42 weeks) who were to undergo amniocentesis.

1. Fifty nine healthy controls (C)
2. Fifteen preeclamptic patients (PE). Twelve patients developed hypertension, edema and/or proteinuria after the 30th week of gestation. In the other 3 patients, PE was superimposed on chronic hypertensive disease. Severe PE i.e. Bp $\geq 160/100$ mm Hg, was diagnosed in 3 patients.
3. Twenty six patients with chronic hypertension (H). These included patients with known chronic hypertensive disease antedating the pregnancy, and those in whom hypertension i.e. Bp $\geq 140/90$ mm Hg became manifest prior to the 20th gestational week. In 8 patients, the hypertension was severe i.e. Bp $\geq 160/100$ mm Hg.
4. Nineteen patients with associated Diabetes mellitus (D). These included 16 class A, and 3 Class B patients.

Informed consent was obtained. Amniocentesis and percutaneous radial artery puncture were performed almost simultaneously while the

patients were still supine. The samples (both arterial blood and AF) were collected anaerobically into 20 ml glass syringes (heparinized for blood collection). Meconium or blood-stained AF samples were discarded. Aliquots of blood and AF were added to chilled sodium fluoride containing tubes. The syringes were immediately sealed and immersed in ice. All samples were transferred immediately to the laboratory. Blood and AF gas analyses were performed with a Radiometer BMS-3-MK-2 blood micro-system. The oxygen and carbon dioxide tensions and pH were measured directly with special precautions for AF (titration at low oxygen tensions). Bicarbonate (Bicarb), of both blood and AF, and blood base excess (BE) were derived from SIGGARD-ANDERSEN alignment nomogram [21]. Measured volumes of blood and AF from the fluoride tubes were added, within minutes, to chilled trichloroacetic acid and the protein free filtrate used for lactic (L) and pyruvic (P) acid determinations using an enzymatic method (lactic dehydrogenase).^{*} All laboratory determinations were performed in duplicate. Packaged computer programs were used to perform the statistical analyses of the data. These included: STUDENT t-test, PEARSON's correlation, TUKEY's multiple comparisons, multiple regression, and multiple partial F test [11, 15].

^{*} Sigma Technical Bulletin 627/826 UV, Sigma Chemical Company, St. Louis, MO. U.S.A.

2 Results

The pertinent clinical data of the patients studied are summarized and compared in Tab. I.

The results of the determinations of the various constituents studied in the arterial blood (Bl) and AF in the 4 groups are given and compared in Tabs. II and III respectively. It can be seen that the pH, pO₂, and Bicarb are lower; whereas pCO₂, L, and P are much higher in the AF than in the blood both in normal and pathologic pregnancies. TUKEY's multiple comparisons test was applied to these data. There were no statistically significant differences (at the 5% level) between the different groups in relation to either the maternal blood or AF constituents studied except, the higher AF-pO₂ in chronic hypertensive patients (Tabs. II and III).

The test was then repeated limiting the statistical analysis to the data from the patients with more severe disease i.e. severe PE (3 patients), Severe hypertension (8 patients), and class B diabetes (3 patients) in comparison with the controls. The only additional statistically significant difference found was the lower blood pH in severe PE (7.34 ± 0.06) as compared to the controls (7.42 ± 0.03).

To study factors influencing AF-pH, multiple regression was calculated using AF-pH as the dependent variable and AF-Bicarbonate, AF-pCO₂ and Bl-pH as the independent variables. The equation describing this relation in normal preg-

Tab. I. Pertinent clinical data of the patients studied.

	Control (C) (59) [*]	Preeclampsia (PE) (15)	Chronic hypertension (H) (26)	Diabetes mellitus (D) (19)	Remarks [†]
Age (years)	23.3 $\pm$ 4.8 ^{**}	20.3 $\pm$ 6.0	28.2 $\pm$ 7.1	28.5 $\pm$ 8.0	Higher in H & D than in C & PE
Gravidity	3.6 $\pm$ 2.4	1.8 $\pm$ 2.3	3.9 $\pm$ 2.3	5.0 $\pm$ 3.4	Higher in D than in PE
Parity	2.2 $\pm$ 2.1	0.7 $\pm$ 2.3	2.7 $\pm$ 2.4	3.7 $\pm$ 3.4	Higher in D than in PE
Gestational age (weeks)	37.5 $\pm$ 2.9	37.3 $\pm$ 2.7	38.4 $\pm$ 1.6	37.7 $\pm$ 1.6	No differences
Mean blood pressure ^{***}	85.9 $\pm$ 7.7	111.1 $\pm$ 12.8	114.3 $\pm$ 9.2	86.9 $\pm$ 7.9	Higher in PE and H than in C & D

^{*} Number of patients in each group.

^{**} Mean $\pm$ S.D.

^{***} Mean blood pressure = Diastolic pressure + 1/3 pulse pressure.

[†] Statistical analysis using TUKEY's multiple comparisons test. Only the significant (at the 5% level) differences between the groups are noted.

Tab. II. Acid base parameters in the blood comparison between the different groups.

	Control	Preeclampsia	Chronic hyper- tension	Diabetes mellitus	Remarks†
paO ₂ (Torr)	99.3 ± 7.8*	96.0 ± 10.7	93.5 ± 8.6	92.9 ± 5.7	N.S.
paCO ₂ (Torr)	28.8 ± 3.7	28.3 ± 2.4	30.3 ± 4.0	29.0 ± 3.6	N.S.
pH	7.42 ± 0.04	7.39 ± 0.06	7.41 ± 0.03	7.41 ± 0.03	N.S.
Bicarbonate (mEq/L)	19.0 ± 2.8	18.0 ± 3.0	19.3 ± 2.3	18.0 ± 1.9	N.S.
Base excess (mEq/L)	-4.2 ± 2.2	-5.0 ± 2.5	-4.2 ± 1.8	-4.5 ± 1.7	N.S.
Lactic acid (mmol/L)	1.316 ± 0.66	1.401 ± 0.61	1.203 ± 0.68	1.155 ± 0.50	N.S.
Pyruvic acid (mmol/L)	0.063 ± 0.04	0.077 ± 0.05	0.068 ± 0.05	0.064 ± 0.04	N.S.

† TUKEY's multiple comparisons test, N.S. No significant difference.

* Mean ± S.D.

Tab. III. Acid base parameters in the amniotic fluid comparison between the different groups.

	Control	Preeclampsia	Chronic hypertension	Diabetes mellitus	Remarks†
pO ₂ (Torr)	23.6 ± 6.0*	—	33.5 ± 6.4	—	S.
pCO ₂ (Torr)	45.4 ± 9.4	44.8 ± 6.5	45.1 ± 5.9	42.8 ± 8.5	N.S.
pH	7.07 ± 0.08	7.02 ± 0.12	7.06 ± 0.08	7.04 ± 0.08	N.S.
Bicarbonate (mEq/L)	12.5 ± 3.0	11.5 ± 3.8	13.1 ± 3.0	11.5 ± 3.2	N.S.
Lactic acid (mmol/L)	8.576 ± 2.20	7.926 ± 2.52	8.395 ± 1.71	8.988 ± 2.98	N.S.
Pyruvic acid (mmol/L)	0.144 ± 0.06	0.095 ± 0.06	0.164 ± 0.12	0.137 ± 0.06	N.S.

† TUKEY's multiple comparisons test. S. Significant N.S. No significant differences.

* Mean ± S.D.

nancy was: $AF-pH = 5.00 + 0.0259 AF-Bicarb + 0.2664 BI-pH - 0.0052 AF-pCO_2$.

In the other 3 groups, the equations were insignificantly different from that of the normal group, as determined by the multiple partial F test [13].

We have previously constructed significance bands that show the anticipated response (with 95% confidence) of BI-pH (H^+) and plasma bicarbonate to varying levels of paCO₂ in normal pregnancy [6]. The BI-pH (H^+), plasma bicarbonate, and paCO₂ values of patients with pathologic pregnancies were plotted on these bands (Figs. 1 and 2). In Fig. 1 all pH values were within the band except those of two patients with severe PE, which were

above the band. These represent superimposed acidosis on the acid base status of normal pregnancy. Fig. 2 shows that values from all but 2 patients; a pre-eclamptic and a chronically hypertensive, were within the band. In these two instances Bicarbonate levels were higher than anticipated.

3 Discussion

Both in normal and abnormal pregnancies studied, the arterial paCO₂, Bicarbonate, and BE were reduced whereas; paO₂, BI-L, BI-P, and BI-pH were slightly increased in comparison with corresponding levels in non-gravid females [6, 10, 20]. The chan-

Fig. 1. Data from the patients with abnormal pregnancies superimposed on the 95% significance band showing the anticipated response of (H^+) to changing $PaCO_2$ in normal pregnancy.

Fig. 2. Data from the patients with abnormal pregnancies superimposed on the 95% significance band showing the anticipated response of HCO_3^- to changing $PaCO_2$ in normal pregnancy.

ges in the maternal blood acid base parameters during normal pregnancy are consistent with a state of „maximally compensated sustained respiratory alkalosis“, as detailed elsewhere [6]. In the present study, the same parameters were not found to be significantly different in the pathologic pregnancies investigated (Tab. II), in agreement with previous studies involving 8 pre-eclamptic and 2 diabetic patients [3, 14]. However, we found that in severe PE the Bl-pH was significantly lower than in normal pregnancy (7.34 ± 0.06 vs 7.42 ± 0.03). In addition, the Bl-pH of 2 out of 3 patients with severe PE were

above the significance band of normal pregnancy (Fig. 1). These findings suggest the existence of a complicating i.e. mixed metabolic acidosis in severe PE. This concurs with a recent report in which it was found that the base deficit was increased in “severe” but not “moderate” PE as compared to normal pregnancy [17]. Blood lactate levels were reported to increase in PE [9]. HANDLER [9] proposed that impaired placental blood flow in severe PE causes the fetus to be more dependent on anaerobic metabolism and to produce more lactate. Also, placental lactate production was reported to be augmented in severe PE [8]. However, we did not find evidence of hyperlactatemia in PE either in the present, or a previous study [4]. An alternative mechanism maybe the cause of the metabolic acidosis. In pregnancy, as H^+ concentration decreases as a result of hyperventilation and consequent hypocapnia, fewer H^+ ions become available for active secretion by the renal proximal tubular cells and less HCO_3^- is reabsorbed or reclaimed to the plasma [2]. This is one of the significant mechanisms whereby the respiratory alkalosis is compensated. We propose that in severe PE, the specific renal lesion [7] interferes in some way with the renal compensatory mechanism. This postulate needs to be further investigated.

The AF-pH was lower than Bl-pH both in the normal and abnormal pregnancies studied. This is attributed to a lower buffering capacity (decreased bicarbonate, and low protein concentration), as well as, a higher concentration of fixed acids; particularly lactic acid, and pCO_2 , as compared to the maternal blood. The equation describing the relation of AF-pH to the other variables indicate that it is influenced by maternal Bl-pH both in normal [5] and abnormal pregnancies.

There have been very few studies of the acid base balance of AF in abnormal pregnancies. In one study, a group of 12 patients with severe “toxemia”, diabetes, Rh sensitization, and post-datism had lower AF-pH and AF-Bicarb and a slightly higher AF- pCO_2 as compared to controls [16]. In a more recent study, AF- pCO_2 was reported to be normal in 13 patients with hypertensive disorders, and 10 with diabetes [1], in agreement with our findings of normal AF-Bicarb in these groups of

patients. In contrast with a previous report of slightly higher AF-L in PE [21], in the present study AF-L was insignificantly lower in PE than in other groups. The only statistically significant difference between the AF acid base parameters studied was the higher AF-pO₂ in pregnant patients with chronic hypertension (Tab. III). One may postulate that in such pregnancies, a compensatory increase in fetal cardiac output occurs that results in an increased cutaneous blood flow and an increased transport of oxygen from fetal blood to AF.

Summary

This study was designed to determine if there are changes in the maternal acid base balance in selected high risk pregnancies that are superimposed on the changes of the normal pregnant state and to determine the effects of intrauterine stress in these abnormal pregnancies on the acid base status of the amniotic fluid (AF).

AF and arterial blood (BI) were obtained almost simultaneously from third trimester pregnant women; 59 healthy controls, 15 pre-eclamptics (PE), 26 with chronic hypertensive disease (H), and 19 with diabetes mellitus (D). Of these, there were 3 patients with severe PE, 8 patients with severe H, and 3 with class B diabetes. All samples were obtained anaerobically. Oxygen and carbon dioxide tensions (pO₂ and pCO₂), and pH were measured directly using a Radiometer BMS-3-MK-2. Bicarbonate (HCO₃⁻), and base excess (BE) were derived from SIGGARD ANDERSEN alignment nomogram. Lactic (L) and pyruvic (P) acids were measured using an enzymatic method (lactic dehydrogenase). The pH, pO₂, HCO₃⁻ were lower, whereas, pCO₂, L, P, were much higher in the AF than in BI in all groups (Tabs. II and III). Using TUKEY's multiple comparisons test, statistically significant differences between the groups were limited to a higher AF-pO₂ in patients with chronic hypertensive disease and to a lower

The absence of other significant changes in the AF acid base parameters suggest that fetal acid base homeostasis is maintained in the studied pathologic conditions. Otherwise the changes must be so subtle that they were not demonstrable within the limits of this type of study. Differences may become apparent when the fetus is exposed to the added stresses of labor [12, 13, 18]. Further studies of AF-L, AF-pCO₂, and AF-pO₂ and the corresponding fetal blood levels during labor and/or at delivery in both normal and abnormal pregnancies are needed.

BI-pH in patients with severe PE. Multiple regression analysis was applied to AF-pH. It was found that it is influenced by maternal BI-pH both in normal and pathologic pregnancies.

The arterial blood pH, HCO₃⁻ and pCO₂ values from the patients in the different groups were plotted on significance bands that show with 95% confidence, the anticipated response of pH, and HCO₃⁻ to varying levels of pCO₂ in normal pregnancy. In 2 out of 3 patients with severe PE the pH was above the band suggesting the superimposition of metabolic acidosis (Fig. 1). This is supported by our finding of a significantly lower BI-pH in severe PE. The metabolic acidosis did not seem to be related to increased arterial lactate levels in these patients. It may possibly be related to derangement of the renal mechanism for maintaining acid base homeostasis, caused by the specific renal lesions of PE. The increased AF-pO₂ in chronically hypertensive patients is postulated to be due to compensatory increase in fetal cardiac output, and secondarily cutaneous blood flow, with consequent increased transport of O₂ from fetal blood to AF.

Although there were no other significant changes in AF acid base parameters in the studied abnormal pregnancies, such differences may become apparent when the fetus is exposed to the added stress of labor.

Keywords: Acid Base equilibrium, amniotic fluid, bicarbonate, carbon dioxide, hypertension, lactate, metabolic acidosis, oxygen, pre-eclampsia, pregnancy in diabetes.

Zusammenfassung

Säure-Basen-Haushalt bei Schwangeren mit Präeklampsie, Hypertonie und Diabetes. Untersuchung des mütterlichen Blutes und des Fruchtwassers

Wir wollten mit dieser Untersuchung herausfinden, ob bei Risikoschwangerschaften Änderungen des Säure-Basen-Gleichgewichts eintreten, die möglicherweise von Veränderungen, wie sie eben in jeder normalen Schwangerschaft stattfinden, überlagert werden. Außerdem sollte der Einfluß des intrauterinen Stress auf den Säure-Basen-Status des Fruchtwassers (FW) bestimmt werden.

Von Schwangeren im 3. Trimenon entnahmen wir nahezu gleichzeitig Fruchtwasser und arterielles Blut (BI). 59 gesunde Frauen bildeten die Kontrollgruppe. 15 Schwangere hatten eine Präeklampsie (PE), 3 davon mit schwerwiegender Symptomatik. 26 Frauen hatten eine chronische Hypertonie (H), die bei 8 von ihnen zu extremen Blutdruckerhöhungen führte. Von 8 Schwangeren mit Diabetes mellitus (D) zeigten 3 einen Diabetes der Stufe B. Alle Proben wurden ohne Luftzutritt entnommen. Der O₂- und CO₂-Partialdruck (pO₂ und pCO₂) sowie der

pH wurden direkt unter Benutzung eines Radiometers BMS-3-MK-2 bestimmt. Die Bikarbonatkonzentration (HCO_3^-) und den Basenüberschuß (=base excess, BE) erhielten wir aus dem SIGGAARD-ANDERSEN-Nomogramm. Laktat (L) und Pyruvat (P) wurden über eine enzymatische Methode (mit Laktatdehydrogenase) bestimmt. Der pH, pO_2 sowie HCO_3^- waren im Fruchtwasser niedriger als im Blut, während pCO_2 , Laktat und Pyruvat im Fruchtwasser höher als im Blut lagen. Diese Aussage gilt für alle Gruppen gleichermaßen (Tab. II und III). Statistisch signifikante Unterschiede gegenüber dem Normalkollektiv ließen sich jedoch nur bezüglich eines hohen pO_2 im Fruchtwasser bei Patienten mit chronischer Hypertonie und hinsichtlich eines niedrigeren Blut-pH-Werten bei Patienten mit schwerwiegenden Präeklampsien feststellen.

Auf die Fruchtwasser-pH-Werte wandten wir eine Regressionsanalyse an und konnten schlußfolgern, daß der pH im Fruchtwasser sowohl in normalen wie auch in pathologischen Schwangerschaften durch den pH im mütterlichen arteriellen Blut beeinflusst ist.

Die pH-, HCO_3^- und paCO_2 -Werte im arteriellen Blut der Patienten aus den verschiedenen Gruppen wurden in Kurven eingezeichnet, die Signifikanzbereiche aus normalen Schwangerschaften umschreiben. Aus diesen Signifikanzbereichen läßt sich mit einer Sicherheit von 95%

der Erwartungswert für den pH bzw. HCO_3^- bei variierenden CO_2 -Partialdrücken bestimmen. Bei 2 der 3 Patienten mit schwerer Präeklampsie lag der pH oberhalb des Bereiches, was auf eine überlagernde metabolische Azidose schließen läßt (Fig. 1). Entsprechend fanden wir einen signifikant niedrigeren Blut-pH bei schwerer Präeklampsie. Jedoch scheint keinerlei Beziehung zwischen metabolischer Azidose und erhöhtem Laktatspiegel bei diesen Patienten zu bestehen. Offensichtlich ist der renale, der Homöostase dienende Mechanismus gestört, wobei die Ursache in der spezifischen, durch die Präeklampsie bedingten Nierenschädigung liegt.

Der Anstieg des pO_2 im Fruchtwasser von chronischen Hypertonikerinnen ist möglicherweise auf eine kompensatorische Zunahme der fetalen Herzarbeit zurückzuführen, die eine gesteigerte Hautdurchblutung zur Folge hat. Hieraus resultiert dann ein gesteigerter Transport von O_2 aus dem arteriellen Blut in das Fruchtwasser.

Für die anderen Säure-Basen-Parameter konnten wir keine signifikanten Unterschiede zwischen den Gruppen und gegenüber dem Normalkollektiv feststellen. Wir nehmen aber an, daß signifikante Änderungen unter Geburtsbedingungen, die eine extreme Streßsituation darstellen, sicher deutlicher werden.

Schlüsselwörter: Bikarbonat, Diabetes in der Schwangerschaft, Fruchtwasser, Hypertonie, Kohlendioxyd, Lactat, metabolische Azidose, Präeklampsie, Säure-Basen-Haushalt, Sauerstoff.

Résumé

Equilibre acido-basique dans les grossesses avec pré-éclampsie, hypertension et diabète.

Examens du sang maternel et du liquide amniotique.

Cette étude a été faite pour déterminer s'il existe des changements dans l'équilibre acido-basique maternel de grossesses sélectionnées «à haut risque», changements qui se superposeraient à ceux des grossesses normales, et quels sont les effets du stress intra-utérin de ces grossesses anormales sur le statut acido-basique du liquide amniotique (AF).

Le liquide amniotique et le sang artériel (BI) ont été prélevés presque simultanément en cours du troisième trimestre de grossesse; 59 contrôles de grossesses normales, 15 cas de prééclampsie (PE), 26 d'hypertension chronique (H) et 19 de diabète mellitus (D). Parmi ces grossesses à haut risque, on a dénombré 3 cas de PE grave, 8 de H grave et 3 de diabète classe B. Tous les spécimens ont été prélevés anaerobiquement. Les tensions d'oxygène et de dioxyde de carbone (pO_2 & pCO_2) et le pH ont été mesurés directement à l'aide d'un radiomètre BMS-3-MK-2. Le bicarbonate (HCO_3^-) et l'excès basique (BE) ont été dérivés du nomogramme d'alignement de SIGGAARD ANDERSEN. Les acides lactiques (L) et pyruviques (P) ont été mesurés à l'aide d'une méthode enzymatique (déhydrogénase lactique). Les pH, pO_2 et HCO_3^- ont été inférieurs, tandis que les pCO_2 , L et P ont été beaucoup plus élevés dans le liquide amniotique que dans le sang artériel de tous les groupes (Tab. II & III). Recourant au test des comparaisons multiples de TUKEY, les différences statistiquement significatives

entre les groupes se sont limitées à un PO_2 du liquide amniotique plus élevé chez les parturientes avec hypertension chronique et à un pH sanguin plus bas chez les parturientes avec pré-éclampsie grave. Une analyse de régression multiple a été appliquée au pH du liquide amniotique. On a constaté qu'il est influencé par le pH sanguin aussi bien dans les grossesses normales que pathologiques.

Les valeurs de pH, HCO_3^- et paCO_2 du sang artériel chez les parturientes des différents groupes ont été relevées sur des bandes significatives avec un degré de précision de 95% et qui illustrent la réaction anticipée de pH et de HCO_3^- aux degrés variables du paCO_2 dans les grossesses normales. Chez deux des trois parturientes avec une PE grave, le pH était au-dessus de la bande suggérant la superposition d'acidose métabolique (Fig. 1). Ce résultat se trouve confirmé par notre observation d'un pH sanguin significativement plus bas en cas de PE grave. L'acidose métabolique n'a pas paru être en corrélation avec des degrés accrus de sel lactique artériel chez ces parturientes. Il est possible qu'elle dépende du dérèglement du mécanisme rénal pour une homeostase acido-basique persistante, causée par les lésions rénales spécifiques de la PE. La hausse de pO_2 du liquide amniotique chez les parturientes avec hypertension chronique est — selon les observations — due à l'augmentation compensatrice du débit cardiaque foetal et, secondairement, au flux sanguin cutané avec le passage consécutivement accru de O_2 du sang foetal au liquide amniotique.

Bien qu'il n'y ait pas eu d'autres changements significatifs dans les paramètres acido-basiques du liquide amniotique des grossesses anormales soumises à examen, il est possible

que ces différences apparaissent quand le fœtus est exposé à une recrudescence du stress du travail d'accouchement.

Mots-clés: Acidose métabolique, bicarbonate, dioxyde de carbone, équilibre acido-basique, grossesse avec diabète, hypertension, liquide amniotique, oxygène, pré-éclampsie, sel lactique.

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Hossam E. Fadel
Department of Obstetrics and Gynecology
Medical College of Georgia
Augusta, Georgia 30902/USA