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Et al.

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Abstract

Objective: In May 2009, after considering short and long-term maternal/child outcomes, the Institute of Medicine (IOM) revised recommendations for gestational weight gain (GWG); however preeclampsia was dismissed due to insufficient evidence. Our objective was to evaluate preeclampsia risk by angiogenic-biomarker profile by both BMI and GWG-adherence. Given numerous studies showing adipose tissue's ability to stimulate angiogenesis, we hypothesized that overweight/obese (OW-OB) women and over-gainers (OG) would have altered angiogenic profiles as compared to underweight/normal-weight (U-N) women and under-/appropriate-gainers (U-AG), respectively.

Methods: Between 5/04-1/06, serial serum specimens collected from 94 women at high preeclampsia risk between 22-36 weeks. Soluble fms-like tyrosine kinase-1 (sFlt1), placental growth factor (PlGF) and soluble endoglin (sEng) measured by ELISA. BMI and GWG adherence categories determined by 1990 IOM recommendations. Within-women correlation and right-skewness handled by estimating linear mixed models for ln-transformed biomarkers and then exponentiating on ln scale (i.e.geometric means). T-test compared means in 3 windows.

Results: Analytic sample included 82 subjects (342 specimens) without multiples or pregnancy-related hypertension diagnosis. Mean sFlt1 lower in all windows in OW-OB compared to U-N - significant only at 22-26wks [506.2(95%CI 438.1-584.9) vs 745.5(95%CI 595.9-932.6) p=0.04] and in OG compared to U-AG with significant comparisons (p=0.05) [22-26wks: 492.1(95%CI 420.1-576.3) vs 691.3(95%CI 574.0-832.6); 27-30wks: 570.1(95%CI488.1-665.9) vs 788.8(95%CI 656.8-947.4)]. Mean PlGF lower in all windows in OW-OB compared to U-N [22-26wks: 430.5(95%CI 359.0-516.3) vs 588.6(95%CI 444.3-779.7) p=0.06; 27-30wks: 475.8(95%CI 398.7-567.8) vs 811.8(95%CI 614.3-1072.9) p=0.005; 31-36wks: 428.5(95%CI 358.0-513.0) vs 724.6(95%CI 548.5-957.1) p=0.01] and in OG compared to U-AG with no significant comparisons. Mean ratio [(sFlt1+sEng):PlGF] trended higher in OW-OB compared to U-N women at 27-30 and 31-36wks and in OG compared to U-AG at 31-36wks; however no windows with significant comparisons.

Conclusion: Findings suggest trends that OW-OB BMI and excessive GWG associated with angiogenic biomarker profiles consistent with higher preeclampsia risk. Exploratory study limited by small numbers. BMI and GWG as potentially modifiable factors merit further investigation for preeclampsia risk alteration.

Background

- In May 2009, after considering short and long-term maternal/child outcomes, the Institute of Medicine (IOM) revised recommendations for gestational weight gain (GWG); however preeclampsia was dismissed due to insufficient evidence.

IOM 2009

- Since change in recommendations, epidemiologic studies have since been published that support an association between GWG adherence and hypertensive disease of pregnancy.

AJOG 2009;200(2):167.e1-7

- Numerous studies have revealed adipose tissue's ability to stimulate angiogenesis

Cardiovascular Res 2008;78(2):286-93

Objective

To evaluate preeclampsia risk by angiogenic-biomarker profile by both BMI and GWG-adherence.

Hypothesis

We hypothesized that overweight/obese (OW-OB) women and over-gainers (OG) would have altered angiogenic profiles as compared to underweight/normal-weight (U-N) women and under-/appropriate-gainers (U-AG), respectively.

Materials & Methods

- **Pregnant subjects <24 weeks gestation enrolled from outpatient prenatal clinics at UMass Memorial Health Care between May 2004 and January 2006.**
- **Each subject had ≥1 of the following risk factors for preeclampsia:**

Inclusion Criteria	RR
Chronic HTN	2.37
Renal Disease/CKD	-----
Pregestational DM	3.56
History of Preeclampsia	7.19
Teen Pregnancy (≤ 18)	2.98
Multi-fetal gestation	2.93 (twins)
	2.83 (triplets)
Obesity (BMI > 30)	2.47
APL Ab Syndrome	9.72
SLE	-----

Duckitt K & Harrington D. BMJ. 2005

- **Subjects recruited** **127**

Exclusions

missing outcomes	3
gestational HTN	5
multiple gestations[a]	25
preeclampsia diagnosis[b]	12
Subjects included in analyses	***82***
	(342 samples)

Excluded due to association with altered angiogenic profile:

[a]Multiple gestations (n=20) ***Maynard et al, AJOG,* 2008;198:200**

[b]Hypertensive diseases of pregnancy (gestational HTN & preeclampsia)

***Moore Simas et al, AJOG, 2007*;197:244.e1-244.e8**

- **sFlt1, PlGF and sEndoglin levels were measured by ELISA**
- **BMI & GWG adherence categories by 1990 IOM recommendations**

Pre-pregnancy BMI Category	Pre-pregnancy BMI* (kg/m^2)	Total GWG at 40 weeks
Underweight (U)	<19.8	28-40 lbs
Normal weight (N)	19.8-26.0	25-35 lbs
Overweight (OW)	26.1-29.0	15-25 lbs
Obese (OB)	>29.0	At least 15 lbs

Adherence defined by GWG and GA @ last prenatal visit subtracted from pre-pregnancy weight; thus preterm and term deliveries included

Statistical Analysis

- Demographic comparisons utilized Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables (see Table 1)
- Within-women correlation and right-skewness handled by estimating linear mixed models for ln-transformed biomarkers and then exponentiating on ln scale (i.e., geometric means).
- Geometric mean and 95% confidence intervals displayed for sFlt1, PlGF and (sFlt1+sEng):PlGF in each of 3 gestational-age windows for UW-N vs. OW-OB BMI and Under-Appropriate vs. Over-gainers (see figures 1-6)
- T-test compared means in 3 windows.

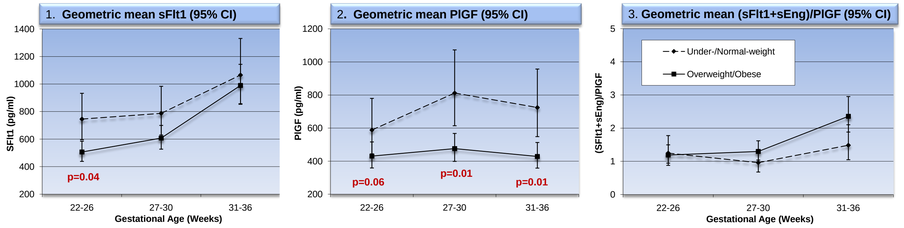
Results

- **Analytic sample included 82 subjects (342 specimens).**
- **See Table 1 for Demographic Comparisons.**
- **BMI Comparisons** (see Figures1–3)
  - Mean sFlt1 lower in all windows in OW-OB compared to U-N (Figure 1)
  - Mean PlGF lower in all windows in OW-OB compared to U-N (Figure 2)
  - Mean ratio [(sFlt1+sEng):PlGF] trended higher in OW-OB compared to U-N women at 27-30 and 31-36wks (Figure 3)
- **GWG Adherence Comparisons** (see Figures 4–6)
  - Mean sFlt1 lower in all windows in OG compared to U-AG (Figure 4)
  - Mean PLGF lower in all windows in OG compared to U-AG (Figure 5)
  - Mean ratio [(sFlt1+sEng):PlGF] trended higher in OG compared to U-AG at 31-36wks (Figure 6)

Table 1. Demographic comparisons

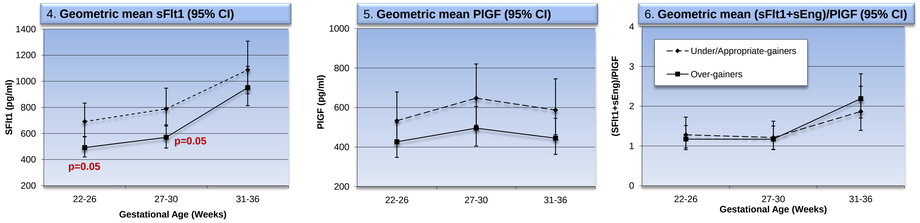
Demographic Characteristics	BMI Categories: Underweight-Normal Mean±SD	BMI Categories: Overwgt-Obese Mean±SD	BMI Categories: P-Value	GWG Adherence Categories: Under/Appropr Gain Mean±SD	GWG Adherence Categories: Over-Gain Mean±SD	GWG Adherence Categories: P-Value
Age (years)	25.9±8.5	31.1±6.6	0.01	29.6±7.9	29.5±7.4	NS
Gravity	2.4±1.7	2.9±1.8	NS	2.9±2.1	2.7±1.5	NS
Living Children	0.8±1.1	1.0±1.0	NS	0.9±1.1	0.9±1.0	NS
GA @ first PNV (wk)	11.8±4.4	12.0±6.0	NS	11.8±4.8	12.0±6.3	NS
SBP @ first PNV (mmHg)	114.0±12.5	119.5±13.7	NS	117.1±14.2	119.1±13.1	NS
DBP at first PNV (mmHg)	67.1±5.1	70.8±9.6	NS	70.0±8.4	69.9±9.4	NS
GA at delivery (wks)	38.6±2.2	38.0±2.7	NS	38.6±2.0	37.9±2.8	NS
Placenta weight (g)	443.8±90.1	443.6±206.9	NS	526.4±155.7	371.3±176.2	NS
	N (%)	N (%)		N (%)	N (%)	
Race/ethnicity			0.05			NS
White	13 (54.2)	35 (60.3)		19 (55.9)	29 (60.4)	
Hispanic	10 (41.7)	13 (22.4)		10 (29.4)	13 (27.1)	
Black	0 (0)	9 (15.5)		4 (11.8)	5 (10.4)	
Other	1 (4.2)	1 (1.7)		1 (2.9)	1 (2.9)	
Smoking Status			NS			NS
Current	1 (4.2)	6 (10.3)		4 (11.8)	3 (6.3)	
Prior Pregnancy	6 (25.0)	9 (15.5)		5 (14.7)	10 (20.8)	
Never	17 (70.3)	43 (74.1)		25 (73.5)	35 (72.9)	
Chronic HTN	3 (12.5)	17 (29.3)	NS	9 (26.5)	11 (22.9)	NS
Pregestational DM	6 (25.0)	22 (37.9)	NS	10 (29.4)	18 (37.5)	NS
Renal Disease	4 (16.7)	1 (1.7)	0.02	5 (14.7)	0 (0)	0.01
Adolescent Pregnancy	8 (33.3)	6 (10.3)	0.02	7 (20.6)	7 (14.6)	NS
History Preeclampsia	4 (16.7)	9 (15.5)	NS	7 (20.6)	6 (12.5)	NS
Lupus	4 (16.7)	2 (3.5)	NS	4 (11.8)	2 (4.2)	NS
Antiphospholipid Syndrome	0 (0)	2 (3.5)	NS	0 (0)	2 (4.2)	NS

Figures 1-3. Angiogenic biomarker profiles comparing under-/normal-weight to overweight/obese at 3 gestational age windows



BMI Category	(# specimen/ # women) 22-26 weeks	27-30 weeks	31-36 weeks
Underweight (<19.8)	5/4	6/3	7/4
Normal weight (19.8-26.0)	22/18	27/18	29/17
Overweight (26.0-29.0)	22/16	23/15	28/14
Obese (>29.0)	47/35	63/37	63/36

Figures 4-6. Angiogenic biomarker profiles comparing under/appropriate gainers to over-gainers at 3 gestational age windows



GWG BMI-specific Adherence Category	(# specimen/ # women) 22-26 weeks	27-30 weeks	31-36 weeks
Under gainer	24/17	24/15	27/14
Appropriate gainer	18/13	25/15	29/15
Over gainer	54/43	70/43	71/42

Limitations

- Small sample size required collapsing of BMI and GWG-adherence categories; thus unable to look at adherence within each BMI category
- Secondary analysis not powered for this exploratory analysis
- Only had total GWG at end of pregnancy

Conclusion

- **Findings suggest trends that OW-OB BMI and excessive GWG associated with angiogenic biomarker profiles consistent with higher preeclampsia risk by end of gestation.**
- **BMI and GWG as potentially modifiable factors merit further investigation for preeclampsia risk alteration.**