

## HbA<sub>1c</sub> in Patients with Polycystic Ovary Syndrome: A Potential Marker of Inflammation

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### Abstract

**Background:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder that is associated with increased inflammation, insulin resistance, and elevated risk of metabolic complications. hs-CRP is the most reliable marker of inflammation in PCOS patients. When hs-CRP is elevated, it can indicate increased risk of cardiovascular disease. The purpose of the study was to determine if a certain value of HbA<sub>1c</sub> in PCOS patients should alert clinicians to increased inflammation (as defined by hs-CRP >2 mg/l), thus potentially be indicative of increased risk of cardiovascular disease.

**Methods:** A cohort study was conducted on female patients between the ages of 20 to 45 years who fulfilled the National Institute of Health criteria for PCOS. De-identified data of 46 patients with PCOS were obtained. All clinical tests were conducted after a 12 hr overnight fast. hs-CRP was measured by latex-enhanced immunonephelometry. Logistic regression analysis was conducted to assess the association between hs-CRP and HbA<sub>1c</sub>.

**Results:** When various HbA<sub>1c</sub> levels were considered, a cutoff of 5.3% correctly classified patients with hs-CRP >2 mg/l at 80.4%. Sensitivity was 83.3% and specificity was 75%.

**Conclusion:** An HbA<sub>1c</sub> cut off of 5.3% may be appropriate to initiate efforts for early detection of increased inflammation as a potential sign of risk for cardiovascular disease.

**Keywords:** Cardiovascular disease, HbA<sub>1c</sub>, hs-CRP, Inflammation, Polycystic ovary syndrome.

**To cite this article:** Mortada R, Kallail KJ, Dong F, Karakas SE. HbA<sub>1c</sub> in Patients with Polycystic Ovary Syndrome: A Potential Marker of Inflammation. *J Reprod Infertil.* 2015;16(4):203-206.

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Received: Oct. 31, 2014

Accepted: Mar.3, 2015

### Introduction

Polycystic ovary syndrome (PCOS) is manifested by the combined presence of hyperandrogenism, chronic oligo- or anovulation, and polycystic ovaries. It is a multifactorial and complex syndrome where hyperandrogenism is the hallmark feature of the disease and thought to be implicated in the genesis of the disorder (1, 2). Most women with PCOS have insulin resistance and the prevalence of the metabolic complications such as type 2 diabetes, dyslipidemia, and coro-

nary artery disease is increased (3-5). PCOS has been described as a proinflammatory state where chronic low-grade inflammation plays a role in the development of metabolic derangements and ovarian dysfunction (6).

C-reactive protein levels are elevated in patients with PCOS and may be a marker of early cardiovascular risk in these patients (7). High-sensitivity C-reactive protein (hs-CRP) is the most extensively studied biomarker of inflammation in cardio-

vascular diseases (8) and thought to be the most reliable circulating marker of chronic low-grade inflammation in PCOS (9). Despite the lack of specificity for the cause of inflammation, there is now a body of evidence linking elevated hs-CRP (>2 mg/l) to risk of cardiovascular disease (10, 11). Certain medications used in prevention and treatment of cardiovascular diseases as well as certain dietary modifications reduce serum CRP and the risk of cardiovascular diseases. Reduced inflammation may be responsible for the beneficial effects of these medications (12, 13).

Since inflammation relates to insulin resistance and several other metabolic disorders seen in PCOS, in this study, an attempt was made to investigate whether the increase of hs-CRP level is associated with a certain cutoff of HbA<sub>1c</sub>.

**Methods**

The study was approved by the university’s Institutional Review Boards at the University of California-Davis and the University of Kansas School of Medicine-Wichita.

Female patients at the University of California-Davis between the ages of 20 and 45 years with a body mass index (BMI) of 25 to 45 kg/m<sup>2</sup>, who fulfilled the NIH criteria for PCOS (amenorrhea or oligomenorrhea and had clinical or laboratory evidence of hyperandrogenism in the absence of any confounding pathology) served as subjects (14). Patients using oral contraceptives, anti-androgens, insulin sensitizers, medications for hyperlipidemia, or any other medications or supplements that affect weight or insulin sensitivity during the preceding two months were excluded. Moreover, those with diabetes mellitus, untreated thyroid disease, any other systemic illness, and those who smoked or drank more than two alcoholic drinks per week were excluded as well. These patients were recruited for a prior study (15) and their de-identified clinical data were used for this analysis.

All clinical tests were conducted after a 12 hr overnight fast. Menstruating women were tested during the follicular phase. A blood sample was obtained to determine HbA<sub>1c</sub> levels. Latex-enhanced immunonephelometry was used to measure hs-CRP. Blood sampling for HbA<sub>1c</sub> and hs-CRP were obtained simultaneously. In menstruating patients, the blood samples were obtained during the follicular phase of the cycle to avoid the effects of hormonal changes on metabolic and inflammatory parameters.

**Statistical analysis:** All analyses were conducted using SAS for Windows (version 9.3, Cary, North Carolina). Descriptive statistics were presented as means and standard deviations for continuous variables and frequencies and proportions for categorical variables. A logistic regression analysis was conducted to assess the association between hs-CRP and HbA<sub>1c</sub>. Area Under the Curve (AUC) was reported to assess the discrimination ability of the model. All tests were two-sided with a p-value of less than 0.05 needed to be statistically significant.

**Results**

A total of 46 subjects were included in the final analysis. The average age was 32.0 (SD=6.4, range=20-45) years. The average BMI was 35.0 (SD=8.2, range=25-49.7); more than half (65.2%, n=30) had a BMI greater than 30. The average HbA<sub>1c</sub> was 5.55% (SD=0.40, range=4.8-6.3). Fifty-two percent (n=24) had normal HbA<sub>1c</sub> levels (HbA<sub>1c</sub> less than 5.7), and 47.8% (n=23) had pre-diabetes (HbA<sub>1c</sub> between 5.7 and 6.4). Almost two-third (65.2%, n=30) had a hs-CRP value greater than 2.

To determine whether any cut off value of HbA<sub>1c</sub> was associated with hs-CRP of greater than 2 mg/l, various HbA<sub>1c</sub> cut offs (ranging from 5.1 to 5.7%) were considered with hs-CRP in a logistic regression analysis to determine the association of these two values. As shown in table 1, the cut off

**Table 1.** Model comparison using different HbA<sub>1c</sub> values

Variable	AUC	Correct (%)	Sensitivity (%)	Specificity (%)	False positive (%)	False negative (%)
HbA <sub>1c</sub> (use 5.1% as the cut off)	0.7021	78.3%	96.7%	43.8%	23.7%	12.5%
HbA <sub>1c</sub> (use 5.2% as the cut off)	0.7792	82.6%	93.3%	62.5%	17.6%	16.7%
HbA <sub>1c</sub> (use 5.3% as the cut off)	0.7917	80.4%	83.3%	75.0%	13.8%	29.4%
HbA <sub>1c</sub> (use 5.4% as the cut off)	0.7583	76.1%	76.7%	75.0%	14.8%	36.8%
HbA <sub>1c</sub> (use 5.5% as the cut off)	0.7083	69.6%	66.7%	75.0%	16.7%	45.5%
HbA <sub>1c</sub> (use 5.6% as the cut off)	0.6750	34.8%	40.0%	25.0%	50.0%	81.8%
HbA <sub>1c</sub> (use 5.7% as the cut off)	0.5896	47.8%	63.3%	18.8%	40.6%	78.6%

Table 2. HbA<sub>1c</sub> cutoff of 5.3% by hs-CRP

HbA <sub>1c</sub>	hs-CRP		Total
	hs-CRP >2 mg/l	hs-CRP ≤2 mg/l	
HbA <sub>1c</sub> >5.3%	25 (86.2%)	4 (13.8%)	29 (100%)
HbA <sub>1c</sub> ≤5.3%	5 (29.4%)	12 (70.6%)	17 (100%)
Total	30 (65.2%)	16 (34.8%)	46 (100%)

of 5.3% had the highest AUC value (0.7917). Table 2 shows the number of subjects with elevated hs-CRP (greater than 2 mg/l) using an HbA<sub>1c</sub> of 5.3% as a cut off value. An HbA<sub>1c</sub> cut off of 5.3% predicted the hs-CRP, 80.4% of the time (25 with high HbA<sub>1c</sub> cut off and elevated hs-CRP and 12 with low HbA<sub>1c</sub> cut off and normal hs-CRP). Thus, increased cardiac risk as measured by hs-CRP was associated with HbA<sub>1c</sub> values that fell within normal limits. Sensitivity was 83.3% and specificity was 75%. A low false positive rate (13.8%) was associated with this HbA<sub>1c</sub> cut off value, further indicating that this cut off may be useful in patients with PCOS to identify their potential for cardiac risk.

### Discussion

Our goal was to identify a cut off of HbA<sub>1c</sub> that would correlate with an increased risk for metabolic and cardiovascular disease. Such an HbA<sub>1c</sub> cut off can be used as an early indicator of increased inflammation and perhaps increased risk of cardiovascular disease. An HbA<sub>1c</sub> of 5.3% predicts elevated hs-CRP with a sensitivity of 83.3% and a specificity of 75%. CRP remains the most reliable marker of inflammation in PCOS patients. When elevated, it can indicate an increase in the risk of cardiovascular disease.

Polycystic ovary syndrome remains one of the most common endocrine disorders in women. Several proinflammatory markers are associated with PCOS. The chronic inflammation in PCOS, as measured by CRP, has used high-sensitivity assays as the most reliable marker (8). CRP is an acute phase reactant produced predominantly by hepatocytes under the influence of cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (16). CRP is produced directly by adipose tissue (17). CRP also plays a functional role by promoting the uptake of lipids into foamy macrophages within atherosclerotic plaques (18). In recent ACC/AHA guidelines, a CRP more than 2 mg/l was maintained as a risk factor for increased risk for cardiovascular disease (19). The proin-

flammatory state of obesity contributes to the promotion of insulin resistance and atherogenesis when present in PCOS. Although the degree of inflammation correlates well with the body mass index and adiposity, lean PCOS patients still maintain increased inflammatory markers as compared to their weight-matched non-PCOS controls (20).

CRP levels can vary during the menstrual cycle, whereas estrogen increase is associated with decrease in CRP and progesterone rise is associated with CRP decrease (21). In our cohort of patients, CRP was measured in the follicular phase whenever possible, but variation in CRP during the menstrual cycle was a potential limiting factor in our study.

### Conclusion

Chronic low-grade inflammation is a common feature of insulin resistant states, including obesity, PCOS, and type 2 diabetes. One would expect that there should be a correlation between HbA<sub>1c</sub> level and the degree of inflammation in non-diabetic PCOS subjects. One would expect that interventions that affect either HbA<sub>1c</sub> or CRP should influence the other variable and any risks that are linked to the elevation of this variable.

Clinicians should be aware that an HbA<sub>1c</sub> even in the normal range, such as 5.3%, could be an indicator of elevated CRP in PCOS patients. Additional diagnostic tests may be necessary in these women to assess the cardiovascular risk factors and the suitable time for initiation of early treatment.

### Acknowledgement

We thank Rogelio U. Almario, MS, for conducting the laboratory assays.

### Conflict of Interest

The authors have no conflicts of interest to declare.

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