

Is Glycosylated Hemoglobin A Marker of Infertility? Prospective Analytic Study

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Abstract

Infertility: Is the inability of a couple to naturally conceive, carry or deliver a healthy child after a year of unprotected intercourse⁽¹⁾. Causes: Female factors :- Problems with ovulation. Blocked fallopian tubes; this can happen as the result of pelvic inflammatory disease, endometriosis, or an ectopic pregnancy. Hormonal problems such as polycystic ovarian syndrome (pcos). In ability of the fertilized egg to implant in the uterus. Cervical hostility. Premature ovarian failure. Age; A women's fertility decline after the age of 30, both in her ability to conceive and her ability to carry pregnancy to term. Male factors: The chief factor in male infertility is sperm quality, the man may have poor motility < affecting its ability to reach ovum. Alcohol, marijuana and other drug abuse can affect sperm quality. Other possible factors include erectile dysfunction and retrograde ejaculation. Female infertility account for one third of infertility cases, male infertility for another third, combined male and female infertility for another 15%, and the remainder of cases are " un explained".

Keywords: Hemoglobin, Marker, Infertility

Introduction

Poly cystic ovary syndrome(PCOS):- Is a common endocrine disorder in women of reproductive age with primary manifestation of infertility¹. menstrual dysfunction, and clinical or biochemical hyperandrogenism (hirsutism, acne, and elevated androgens), obesity². Its other associated with hyperlipidemia and impaired glucose tolerance³. The ovaries in woman with PCOS are usually large⁽³⁾ and full of cysts, although they may not have symptoms. About 6%-10% of women have PCOS .To be diagnosed with PCOS, a women must have at least one of the clinical signs mentioned above. It is generally believed that PCOS has a genetic⁴ compenent that is influenced by environmental factors such as diet and exercise. Obesity increase the insuline resistance that often occure with women who have PCOS a hormonal imbalance⁶. Their ovaries and adrenal glands produce more androgens, specifically testosterone, and often less estrogen and progesterone than normal.

Pathophysiology: The frequency of obesity in women with anovulation and PCOS has been reported to be from 35%-60%^{6,7}, obesity is associated with three alterations that interfere with normal ovulations , and

weight loss improves all three:

- 1- Increased peripheral aromatization of androgens to estrogens.
- 2- Decreased level of sex hormone-binding globulin(SHBG), resulting in increase levels of free estradiol and testosterone.
- 3- Increased insulin level that can stimulate ovarian stromal tissue production of androgen⁵.

The ovary does not secrete increased amounts of estrogen and estradiol level are equivalent to early follicular phase concentration, circulating estrone levels are slightly elevated. The increased total estrogen is due to peripheral conversion of the increased amount of androsteredione to estrone. Both estrone and estradiol continue to be secreted in significant, although low amount. The level of sex hormone binding globulin(SHBG) are controlled by a balance of hormonal influences on its synthesis in the liver ; testosterone is inhibitory, estrogen and thyroxine are stimulating. In an ovulatory women with POCS, there is an approximately 50% reduction in circulating levels of SHBG, a response to the increased testosterone, and in patients with hyperinsulinemia due to direct insulin

effect on the liver⁷. There is increase insensitivity of the pituitary to releasing hormone stimulation, manifested by an increase in LH pulse amplitude and frequency, but mainly amplitude, this can be attributed to increase level of free estradiol because of the significant decrease in SHBG. The increase LH secretion as expressed by the LH:FSH ratio is positively correlated with the increased free estradiol^{8,9}. The lower FSH levels represents the sensitivity of the FSH negative feed back system to the elevated estrogen, both free estradiol and estrone formed peripheral conversion of androstendones. Because the FSH levels are not totally depressed, new follicular growth is continuously stimulated, but to the point of full maturation and ovulation¹⁰, follicular life span may extend several months in the form of multiple follicular cysts, 2-10mm in diameter (some can be as large as 15mm). these follicles are surround by hyperplastic theca cell, often lutenized in response to the high LH levels. As various follicles undergo atresia, the tissue derived from follicular atresia is also sustained by the steady state and now contributed to the stromal compartment of the ovary. It is not surprising that this functioning stromal tissue secrete significant amount of androstendione and testosterone, the usual production of theca cells. In response to the elevated LH, the androgen production rate is increased.

Insulin Resistance:

Is defined as a reduced glucose response to a given amount of insulin⁽¹¹⁾. There are several mechanism for the state of insulin resistance: peripheral target tissue resistance, reduced hepatic clearance, or increased pancreatic sensitivity⁽¹²⁾. The clinical presentation of patients with insulin resistance⁽¹³⁾ (whether they have impaired glucose tolerance or diabetes mellitus) depend on the ability of the pancreas to compensate for the target tissue resistance to insulin. At first, compensation is effective and the only metabolic abnormality is hyperinsulinemia. In many patients, the beta cells of the pancreas eventually fail to meet the challenges, and decline insulin levels lead to impaired glucose tolerance and type II non insulin-dependent diabetes mellitus.

Indeed, Beta cell dysfunction can be detected in women with PCOS even before the appearance of glucose intolerance.

Overall Goals of Treatment

- 1- Induction of ovulation to achieve pregnancy.

- 2- Protect the endometrium against the effects of unopposed estrogen.

- 3- Reduce the production and circulating levels of androgens.

- 4- Support life style changes to achieve normal body weight.

- 5- Avoid the effects of hyperinsulinemia on the risks of cardiovascular disease and diabetes mellitus,

- 6- Lower the risk of cardiovascular disease.

The clinical consequences of persistent anovulation

- 1- Infertility.

- 2- Menstrual bleeding problems, ranging from amenorrhea to dysfunction uterine bleeding.

- 3- Hirsutism, alopecia, and acne.

- 4- An increase risk of endometrial cancer and, perhaps, breast cancer.

- 5- An increase risk of cardiovascular disease.

- 6- An increased risk of diabetes mellitus in patients with insulin resistance.

Glycosylated haemoglobin (HbA1c)¹⁴.

Is found by covalent binding of glucose to the N-terminal Valine of the β -chain in the haemoglobin molecule throughout the life time of the erythrocyte.

In the clinical control of diabetic patients, HbA1c serves as an estimator of the time-averaged blood glucose concentration in the proceeding 3-12 weeks.

As a diagnostic tool, HbA1c may have advantage in relation to other methods, and a glycosylated proportion of 7.0% or higher has been proposed as indicative of the need for pharmacological intervention.

Subjects and Method

This is a prospective study carried out at the Maternity and Paediatrics Teaching Hospital in Al-Najaf, during the period between first January 2004 to 30th September 2004. A total of 50 patients were included in this study. They were selected from patients consult out-patient unit as first time planning for pregnancy without previous reproductive experience and patients consult infertility unit after one year of primary infertility for

the first time. 20-30 years old subjects who living with a partner were weighed in light clothes with no shoes and height has been measured ; body mass index was calculated by weight(kilograms) divided by squared height(meters). 6-months retrospective menses calendar was obtained to define of an approximated menstrual irregularity. A serum sample was frozen for later analyses of prolactin.

The measurement of HbA1c was included in the protocol from Jan 2004.

HbA1c was determine in capillary whole blood or venous blood using an immunoturbidmetric assay.

Those whom excluded from the study:

- 1- Those women had diagnosed diabetes mellitus.
- 2- Weight greater than 140 Kg.
- 3- Smoker.
- 4- Those on hormonal therapy.
- 5- Those with insulin sensitizing agents.

Results

A total of 60 patients were available for analysis. Independent t-test had been applied in statistical analysis

at level of significance P,0.05.

SPSS statistical process used V.10.

P>0.05 not significant.

P< 0.05 significant differences.

Table (1):Relationship between Body mass index of 50 subjects with their mean glycosylated haemoglobin.

Group	Number of subject	Mean value of HbA1c	SE mean	Sig. (2-tailed)
BMI<25	13	6.3538	0.6233	0.021 *
≥25	37	8.8973	0.5909	0.006

* significant at P value <0.021

50 subject were weighted in light clothes no shoes and weight(kilograms) divided by squared height(meters) with measurement of HbA1c. A high body mass index was significantly associated with high HbA1cas been shown in table (1) with P. value<0.021.

Table (2) : Relationship between regularity of the menstrual cycle and the mean value of HbA1c.

Regularity of menstrual cycle	Number of subject	Mean value of HbA1c	SE mean	P.value
Regular	22	5.8773	0.2417	0.0001
Irregular	28	9.8926	0.7900	

6-months retrospective menses calendar was obtained to define an approximated menstrual irregularity.

Irregularity of the cycle was significantly associated with high HbA1c With P.value<0.0001.

Table(3): Relationship between the ultrasound finding which related to PCOS and the mean value of HbA1c

PCOS u/s finding	No.	Mean	SE mean	Sig. (2-tailed)
Not present	29	7.7862	0.5258	0.496*
Present	21	7.2381	0.4940	0.494

* no significant association at P.value>0.05.

(Independent sample Test)

Ultrasound examination of those 50 subject reveal presence of ultrasonic finding of polycystic ovary syndrome in (21) of the subject (27 of the total with history of primary infertility not receive treatment till now).

Table (4): Relationship between S.Prolactin level and mean value of HbA1c

S.prolactin level	Number of subject	Mean value of HbA1c	SE mean	Sig. (2-tailed)
Normal	17	8.5059	0.9150	0.272 *
Abnormal	10	9.3900	1.4794	

* no significant association at P.value>0.05.

A serum sample was frozen for later analysis of prolactin for those 27 subjects (whose had history of primary infertility) show 10 of them only presented with biochemical prolactinemia while the rest 17 with normal level. There is no significant association between high prolactin level and high HbA1c with P. value of 0.272.

Discussion

The results indicated that females HbA1c may be a marker of infertility. The level of HbA1c differed significantly between the East and West centres (mean 4.83 versus 4.65 P<0.0005). All couples at the East centre were interviewed at the hospital and HbA1c was measured simultaneously from a capillary blood sample, while for the majority of samples at the west

centre(70%), a sample of various blood sample obtained for later analysis at the laboratory, this may explain the observed differences between the centres.

Possible Physiological mechanisms: Polysystic ovary syndrome(PCOS) is characterized by enlarge ovaries containing an increased number of follicles, and a hyperandrogenic hormone profile involving increased plasma concentrations of testosterone and luteinizing hormone(LH), decreased serum hormone binding globulin(SHBG) and hyperinsulinism¹⁵⁻¹⁷. The prevalence of PCOS syndrome among premenopausal women has been estimated as 5-8%, but usually PCOS diagnosed only when women seek medical advice for hirsutism, oligomenorrhea or infertility¹⁷, using ultrasound detection methods, the prevalence of an ovarian morphology typical of PCOS was shown to be approximately 20% in population samples of adult women and a considerable proportion had a hyperandrogenic hormone profile^{18,19}. These women generally have a normal menstrual and normal body mass index. PCOS has no single organic aetiology, but chronic overstimulation of ovarian steroid synthesis caused by insulin or insulin-like growth factor secondary to decrease insuline sensitivity may be a central feature of the complex hormonal dysregulation leading to this syndrome¹⁶. In this present study only a single blood sample was obtained, irrespective of the timing with respect to the menstrual cycle. A high concentration of HbA1c was associated with a high body mass index. A high concentrate of HbA1c was associated with irregularity of cycle and this differ from the result obtained by Niels Henrick I Hjollund , Tina Kold Tensen, Department of occupational Medicine, Aarhus University Hospital,Norrebrogade, a following study of first time pregnancy planners. HbA1c was not related to ultrasonic finding of PCOS, s-prolactin level. This similar to the result obtained by Department of Gynecology and Obstetrics, Aarhus University Hospital , Aarhus , Denmark,a following study of first pregnancy planners.

Conclusion

Female infertility account for one third of infertility cases, male infertility for another third, combined male and female infertility for another 15%, and the remainder of cases are “ un explained”.

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Maternity and children hospital in Al- D iwaniayah, Iraq and all experiments were carried out in accordance with approved guidelines.

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