British Journal of Medicine & Medical Research
4(3): 889-897, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Insulin Resistance in Infertile Sudanese Patients with Poly cystic Ovarian Syndrome (PCOS) at Laparoscopy

Wisal O. M. Nabag[1], Eshraga A. Farajalla[1] and Mohamed A. A. El Sheikh[2]

[1]Department of Obstetric and Gynecology, Alziem Alazhari University P.O BOX 1432, Khartoum North 13311, Sudan.
[2]Department of Obstetric and Gynecology, University of Khartoum, Sudan.

Authors' contributions

Author WOMN contributed in design and conducting the study as well as writing the manuscript draft; author EAF conduct the laboratory investigations and author MAAES contributed in design of the study as well as writing and editing the manuscript. All authors read and approved the manuscript content.

Original Research Article

Received 2nd July 2013
Accepted 14th September 2013
Published 23rd October 2013

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a complex, heterogeneous disorder of uncertain etiology, characterized by irregular menses, chronic anovulation, infertility, hyperandrogenism, and insulin resistance.
Aims: To determine insulin resistance in infertile Sudanese patients with PCOS and evaluate its significant relation ship to infertility.
Method: A hospital based transversal study was conducted at the Minimal Access Gynecology Surgery (MAGS) unit at Omdurman Maternity Hospital from June 2010 to August 2012 .61 infertile patients with PCOS using Rotterdam 2003 definition and who did not conceive after diet, lifestyle and clomiphene as study group and 61 normo-ovulatory infertile patients with normal ovaries served as a control group at laparoscopy, their serum were sent to the laboratory for estimation of fasting glucose and insulin levels, and then calculation of homeostatic model assessment (HOMA) and p value.
Results: 44(73%) out of the 61infertile patients with PCOS were young, obese with BMI>30, hirsutism was seen in 45 (73.5%) and acne was observed in 42 (70%). Fasting

**Corresponding author: Email: wisnab3@yahoo.com;*

blood glucose (FBG) of 100-125 mg/dl, was encountered in 18(30%) and 3 were diabetic (FBG >125). Fasting insulin level was not significantly elevated in the study group, while Insulin resistance calculated using HOMA. Mean HOMA in the obese PCOS group was significantly higher than in the obese normal ovary group (2.68 ± 2.19 versus 1.26 ± 1.05, P = 0.005).

Conclusion: The majority of the study population was young, obese and had insulin resistance This finding may have important implications in the short term regarding reproductive performance, and in the long term regarding type 2 diabetes and cardiovascular complications

Keywords: PCOS; Laparoscopy; Insulin Resistance; homeostatic model assessment (HOMA).

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders for pre menopausal women with a prevalence rate of 4–12% [1]. PCOS is characterized by irregular menses, chronic anovulation, infertility, hyperandrogenism, and insulin resistance [2]. It is the number one cause for female infertility, according to the Centers for Disease Control and Prevention [3]. In 1991, Poretsky and Nestler found insulin to be an effecter of ovarian and adrenal steroid metabolism, and postulated the paradox of insulin-induced hyperandrogenism within insulin-resistant states [4]. In addition to being involved as a predisposing factor for type-2 diabetes, insulin resistance plays a key role in the pathogenesis of PCOS [5]. One of the major biochemical features of polycystic ovary syndrome is insulin resistance accompanied by compensatory hyperinsulinemia The hyperandrogenism of polycystic ovary syndrome means increasing ovarian androgen production, particularly testosterone and decreasing serum sex hormone binding globulin concentration resulting in acne and Hirsutism [6]. The symptoms and severity of the syndrome vary greatly among affected women [6]. The high levels of androgenic hormones interfere with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, recurrent pregnancy loss, and infertility [2]. Like women without PCOS, women with PCOS who are ovulating may be infertile due to other causes than that related to anovulation like tubal damage due to sexually transmitted diseases.

Women with PCOS have an increased risk of developing type 2diabetes. However, before the onset of diabetes, the blood glucose is usually under control. As such, it is normal for a woman with PCOS to have a fasting blood glucose of 85 to 100 mg/dL, which falls within the normal range of less than 100 mg/dL [7]. Fasting blood glucose of 100 to 125 mg/dL is pre-diabetic stage. Diabetes is diagnosed when the fasting blood sugar is higher than 125 mg/dL[7].. American Diabetes Association suggests that people with this condition should have their blood sugar tested every two years [8].

For overweight, anovulatory women with PCOS, weight loss and diet adjustments, especially to reduce the intake of simple carbohydrates, are associated with resumption of natural ovulation. For those who after weight loss still are anovulatory or for anovulatory lean women, then the ovulation-inducing medications clomiphene citrate [9] and FSH are the principal treatments used to promote ovulation. The anti-diabetes medication metformin was recommended treatment for anovulation [9] but it appears less effective than clomiphene [10]. Ovarian diathermy is a surgical treatment; it thought to reduce the amount of androgen

secreting tissue in the ovaries leading to resumption of ovulation in up to 80%of women with effects lasting six to nine months [11].

This is the first study done in Sudan .The objective of the study is to determine insulin resistance in infertile Sudanese women with PCOS and evaluate its significant relation ship to infertility.

2. MATERIALS AND METHODS

2.1 Population and Study Procedures

This is a hospital based transversal study conducted during the period from the10th June 2010 to 28th August 2012. The study included 61 infertile women diagnosed as PCOS using Rotterdam 2003 definition and who did not conceive after diet, lifestyle and clomiphene so laparoscopy was advised as diagnostic procedure for their infertility and management by ovarian drilling. The patients who have the following diseases were excluded from the study: hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia (abnormal 17-hydroxyprogesterone level), pituitary insufficiency, pituitary tumor, and known diabetes. The control groups were 61 infertile patients with regular cycle undergoing laparoscopy for investigation of infertility and they had normal ovaries and not known to be diabetic. They were matched for age, and ethnicity, however the weight (BMI) of the study group was noted to be higher than the (BMI) of the control group. The patients were usually referred to MAGS by gynecologists from our own hospital, other local hospitals, Family Planning Clinics and the private sector.

Every patient was counseled and gave an informed consent prior to participating in the study, which had been approved by the Ethics Committee, Faculty of Medicine Alziem ALazhari University. Full history concerning their age, type and duration of their infertility, menstrual pattern, acne and hirsutism were reported then their weight and height were recorded and the body mass index (BMI) was calculated. Both patients and controls had an overnight fast of 10-12 hours. 5 ml venous blood was withdrawn, on the same day of admission to the hospital. Out of this 1.5 ml was transferred to a tube containing sodium fluoride and EDTA for glucose estimation. The reminder of the sample was allowed to clot in a plastic tube. After centrifugation clear serum was stored in plastic cups at -20Co for insulin estimation. The sera were transported to Ahmed Gasim Hospital for further study as detailed below.

2.2) Laparoscopy confirmed PCO and drilling: Laparoscopy and dye test were performed as day surgery in the usual manner under general anesthesia. Pelvic adhesions per tubal, per ovarian, massive pelvic adhesions, frozen pelvis, per portal adhesions and endometriosis were reported. Tubal patency was confirmed with free spillage of Methylene blue dye from the fimbrial ends. At laparoscopy the ovaries have white thickened capsules and are often rounded. Bilateral ovarian drilling was performed with electro cautery using dipolar current at 40 strength and 40 seconds for each puncture and then clomifene and metformin were prescribed for 9 months, with follow up regarding their cycle and pregnancy.

2.3 Laboratory Methods

To determine the level of glucose in the serum 1 ml from the reagent (Bio-system) and 20uL from the sample and STD were mixed, incubated for 10 minutes and then read at 520 nm.

Calculation of: The concentration of STD =O.D of sample/O.D of STD X = 100mg/dl [12]. Insulin measurement require first to prepare the working reagent ,add the substrate I& II, make dilution then add the sample & calibrate the result. The normal reference range is 1.1-17 um/ml [13]. Insulin resistance is estimated by HOMA, a method used to quantify insulin resistance and beta-cell function. It was first described under the name HOMA by Matthews et al. in 1985. The approximating equation for insulin resistance used a fasting plasma sample, and was derived by use of the insulin-glucose product, divided by a constant. Insulin is given in mU/L. Glucose measured in mg/dl [14]: HOMA levels of less than 2 is normal, 2 or more is moderately high and over 3.5 is high.

$$\frac{\text{Glucose x insulin}}{405}$$

The data was analyzed using statistical Package for the Social Science (SPSS) and summarized using the percentage. Mean and standard deviation (SD) of the fasting insulin and HOMA as well as P were calculated from mean and SD by using Students t distribution Excel TDIST(x, n-1 degrees freedom, 1 tail) (P=<0.05 is significant)

3. RESULTS

Sixty one infertile Sudanese women with PCOS were included studied. Their age was ranged between 17 to 40 years and 44(73%) had an age range of 20-29 years (Table 1). (90%) had primary infertility with patent tubes, and fertile husbands 40(65.5%) out of 61 in the control group had blocked tubes which explained their infertility while 21(34.5%) had patent tubes, the study group had higher body weight and BMI (29.5 ± 6.0) compared with the control (average BMI: 21.7 ± 3.2). Forty one (65.5%) of the 61 women was obese (BMI >30) as shown in Fig. 1. Table 1 and 2 show the fasting blood glucose levels and their relation to obesity in both the study and control groups; only three women were considered diabetic and they were obese. The clinical features of PCOS among the study population were, prolonged cycle in 53(86%), hirsutism in 45 (73.5%) and acne in 42 (70%) while in the control group these clinical presentations were low or even absent (Fig. 2), The classical triad in the control group are almost absent because they had normal ovaries and so their androgen level is normal.

Fasting insulin level was measured, mean and standard deviation were determined for both case and control groups, P value was calculated and was found to be 7.6, 4.3, 1.8 and 2.8 respectively all of them were not significant as shown in Table 3. Mean HOMA in the obese PCOS group was significantly higher than in the obese normal ovary group (2.68 ± 2.19 versus 1.26 ± 1.05, P = 0.005). P value was calculated from mean and standard deviation (SD) for HOMA and was found to be 0.12 and 0.14 in non obese case and control group respectively as shown in Table 4

Table 1. Fasting blood glucose in PCOS patients by age

Age Group	<100(mg/dl)	100--125(mg/dl)	>125(mg/dl)	Total
15---19	1	1	0	2
20---24	20	2	0	22
25---29	13	8	1	22
30--34	6	5	1	12
35 --40	0	2	1	3
Total	40(65%)	18(30%)	3(5%)	61(100%)

Table 2. Fasting blood glucose in patients with PCOS and control

	PCOS			Control		
Patients	Total No. PCOS	No of Obese	No of non Obese	Total No. control	No of Obese	No of Non Obese
<100(mg/dl)	40(65%)	23	17	55(90%)	4	51
100 - 125(mg/dl)	18(30%)	15	3	5(8%)	3	2
>125(mg/dl)	3(5%)	2	1	1(2%)	1	0

Note: 4 (>125) their age group was more than 35 years

Table 3. Fasting insulin level in both case and control group

	PCOS		Control	
Patients	Obese	Non Obese	Obese	Non Obese
Mean	7.63	6.65	3.18	5.72
SD	±6.85	±3.81	±4.4	±4.25
(*P* = .05) significant	7.6	4.3	1.8	2.8

Table 4. HOMA in the case and control group

	PCOS		Control	
Patients	Obese	Non Obese	Obese	Non Obese
Mean	2.68	1.87	1.26	1.28
SD	±2.19	±1.3	±1.05	±1.3
(*P* = .05) significant*	0.005*	1.21	0.28	0.14

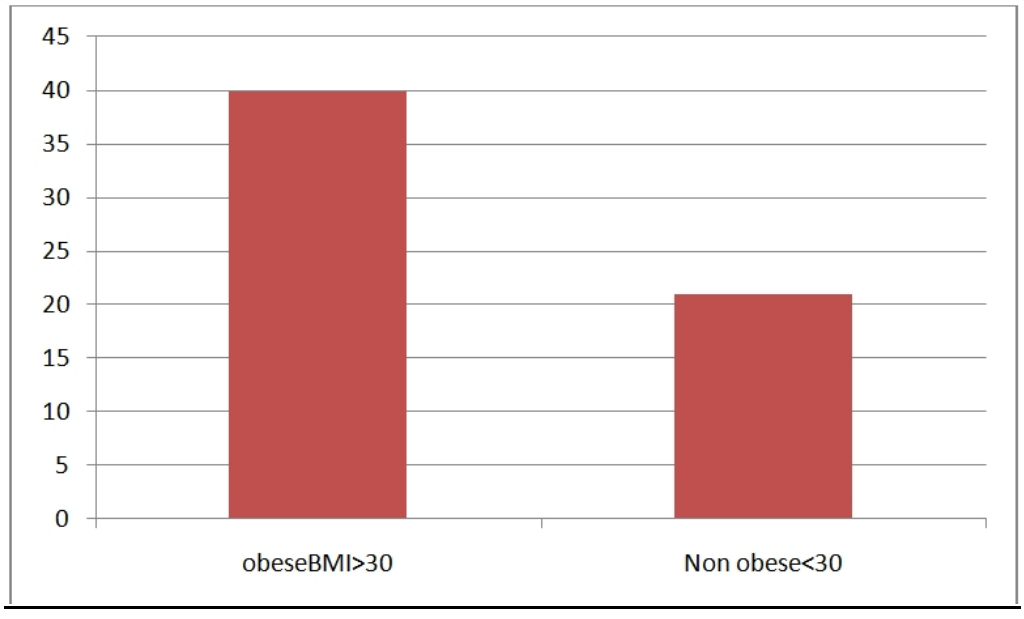

Fig. 1. Body Mass Index (BMI)of patients with PCOS

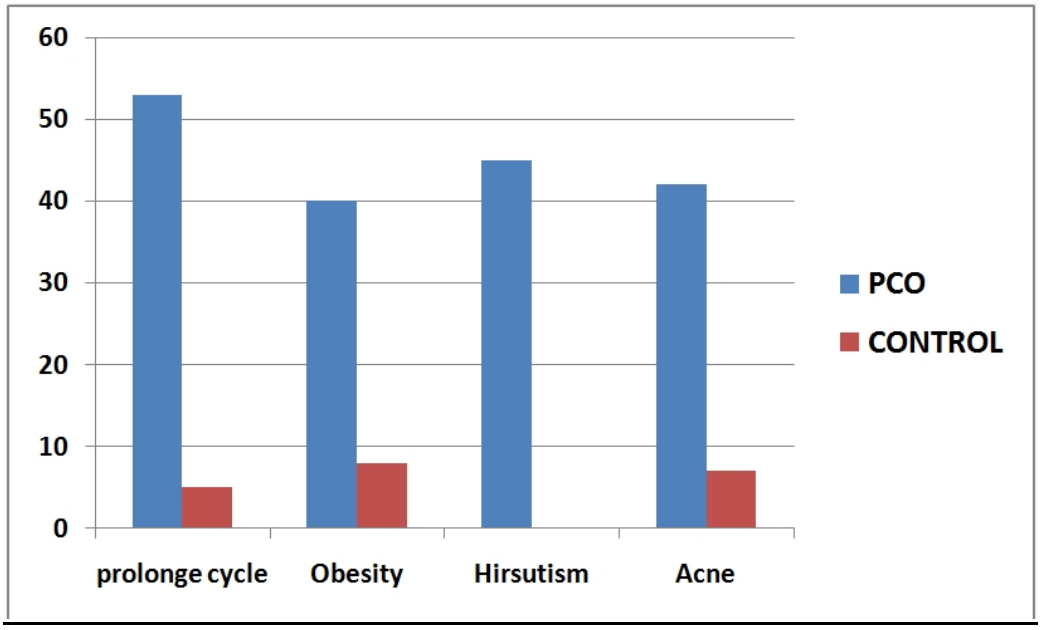

Fig. 2. Clinical findings of patients with PCOS and control

4. DISCUSSION

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders in women of reproductive age 12—45 years [15]. It is a complex, heterogeneous disorder of uncertain etiology. The classic triad of the PCOS includes Hirsutism, menstrual dysfunction, and obesity. The clinical severity largely determined by obesity [16,17]. Infertility associated with PCOS has been attributed to numerous factors, including oligo-anovulation, dysfunctional Gonadotrophin secretion, elevated systemic and/or local ovarian androgen levels, and dysfunction of any or several ovarian growth factors and their binding proteins. Recent research has focused on systemic and local effects of insulin resistance and its secondary effects: systemic, metabolic and ovarian [14]. he majority of our study population (73%) were young and had normal fasting blood glucose (FBG).However the process of rising FBG and insulin happened gradually especially in the obese women .18 patients of study group are in pre diabetic stage compared with 5 in the control group. Our results were consistent with the diagnostic criteria of National Institutes of Health (NIH) in 1990 that showed evidence of hyperandrogenemia in three-quarters of patients with PCOS [17].

A review published in 2010 concluded that women with PCOS had an elevated prevalence of insulin resistance and type II diabetes, even when controlling for body mass index (BMI [18,19]. The principal features are anovulation, resulting in irregular menstruation, amenorrhea, ovulation-related infertility, and polycystic ovaries; excessive amounts or effects of androgenic hormones, resulting in acne and Hirsute; and insulin resistance, often associated with obesity, Type 2 diabetes, and high cholesterol levels [8].

Elevated blood sugar and insulin values do not predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise [20]. Fasting insulin level was not significantly elevated in the study group. A mathematical derivation known as the HOMAI, calculated

from the fasting values in glucose and insulin concentrations is more sensitive [13]: HOMA was found to be highly significant in obese patients because it allows a direct and moderately accurate measure of insulin sensitivity [9]. Obesity in PCOS patients can make insulin resistance worse. This may then cause the level of insulin to rise even further. High levels of insulin can contribute to further weight gain producing a 'vicious cycle'. Losing weight, although difficult, can help break this cycle [21]. While in the control group P value for HOMA was not significant because the majority, were non obese with normal ovaries.

The chance of becoming pregnant depends on how often the patient ovulates. Some women with PCOS ovulate infrequently, others not at all. Metformin is a drug that is commonly used to treat people with type 2 diabetes. It makes the body's cells more sensitive to insulin [10] this may result in a decrease in the blood level of insulin which may help to counteract the underlying cause of PCOS and then increase chance of ovulation. The United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin when other therapy has failed to produce results [22].

The patients did not conceive after diet, lifestyle and cloimiphene so they underwent laparoscopy and ovarian drilling followed by cloimiphene and metformin. 60% of the patients regain regular cycle as the drilling decreases the level of androgen, so the patient regained their cycle and ovulation [11]. The pregnancy rate among study group was 35% within the first 9 months.

5. CONCLUSION

The majority of the study population were young, obese with FBG of >100mg/dl in 21(34.4%) and had insulin resistance using HOMA which is more sensitive than fasting insulin level alone. This finding may have important implications in the short term regarding reproductive performance, and in the long term regarding type 2 diabetes and cardiovascular complications. They underwent laparoscopy and ovarian drilling followed by cloimiphene and metformin with good out come regarding their cycle and pregnancy.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dunaif A, Thomas A: Current concepts in the polycystic ovary syndrome. Annu Rev Med. 2001;52:401-419.
2. Ehrmann DA, Barnes RB, Rosenfield RL. Polycystic ovary syndrome as a form of functional ovarian hyperandrogenism due to dysregulation of androgen secretion. Endocr Rev. 199516:322-353.
3. The Centers for Disease Control and Prevention; Infertility FAQ's; December 28, 2009
4. Poretsky L: On the paradox of insulin-induced hyperandrogenism in insulin-resistant states. Endocr Rev. 1991;12:3-13.
5. Polonsky KS, Sturis J, Bell GI Seminars in Medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus - a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med. 1996;334:777-783.
6. Polycystic ovary syndrome.
   Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001408/.
7. Womenshealth.gov; Polycystic Ovary Syndrome: Frequently Asked Questions; March 17, 2010.
8. American College of Obstetricians and Gynecologists P.O. Box 96920 Washington, DC 20090-6920 Phone. 2002;638-5577. Available: http://www.acog.org/
9. Mayo Clinic Staff. Polycystic Ovary Syndrome – All. MayoClinic.com. Mayo Clinic. Available:http://www.mayoclinic.com/health/polycystic-ovary-syndrome/DS00423/METHOD=print&DSECTION=all. Retrieved 15 November 2011.
10. Legro RS, Barnhart HX, Schlaff WD. Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome. N Engl J Med. 2007;356(6):551-66. doi:10.1056/NEJMoa063971. PMID 2007;17287476
11. FarquharC,Liford RJ ,Majoribanks J,Vandekerckhovep(Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome.Cochrane Database Syst Rev.Jul18;(3):2007CD001122.
12. Lab Tests Online .Peritoneal Fluid Analysis 2008.www.labtestsonline.org/understanding /analytes/peritoneal/test.html.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC "Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.". Diabetologia. 199528 (7): 412–9. doi:10.1007/BF00280883. PMID 3899825.
14. Goldenberg N, Glueck C. Medical therapy in women with polycystic ovary syndrome before and during pregnancy and lactation. Minerva Ginecol. 2008;60(1):63–75. PMID 18277353.
15. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Medicine (Bio Med Central). 2010;8:41. doi:10.1186/1741-7015-8-41. Available: http://www.biomedcentral.com/1741-7015/8/41. Retrieved 14 November 2011.
16. Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. Endocrine 30 (August 2006).(1):19–26. doi:10.1385/ENDO:30:1:19. PMID 17185788.
17. Huang A, Brennan K, Azziz R. Prevalence of hyperandrogenemia in the polycystic ovary syndrome diagnosed by the National Institutes of Health 1990 criteria. Fertil. Steril. 93 (6): 1938–41. doi:10.1016/j.fertnstert.2008.12.138. PMC 2859983. PMID(April 2010). 19249030.
    Available: www.ncbi.nlm.nih.gov/pmc/articles/PMC2859983/.

18. Richard Scott Lucidi ("Polycystic Ovarian Syndrome". eMedicine. http://emedicine.medscape.com/article/256806-overview#showall25 October 2011). Retrieved 19 November 2011.
19. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 16 May 2010);(4):347–63. doi:10.1093/humupd/dmq001. PMID 20159883.
20. Balen A. Metformin therapy for the management of infertility in women with polycystic ovary syndrome" (PDF). Scientific Advisory Committee Opinion Paper 13. Royal College of Obstetricians and Gynaecologists. Available: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SAC13metformin-minorrevision.pdf. Retrieved 2009-12-13.
21. Polycystic Ovarian Syndrome Treatment & Management. eMedicine. Available: http://emedicine.medscape.com/article/256806-treatment#showall. Retrieved 19 November 2011.
22. National Institute for Health and Clinical Excellence. London, 200411 Clinical guideline 11: Fertility: assessment and treatment for people with fertility problems.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=306&id=12&aid=2339