



Review

Preventing endometrial cancer risk in polycystic ovarian syndrome (PCOS) women: Could metformin help?



Mohamad Nasir Shafiee ^{a,b,*}, Gulafshana Khan ^a, Rina Ariffin ^b, Jafaru Abu ^c, Caroline Chapman ^d, Suha Deen ^e, David Nunns ^c, David A. Barrett ^f, Claire Seedhouse ^g, William Atiomo ^a

^a The Division of Obstetrics and Gynaecology and Child Health, School of Medicine, D Floor, East Block, Queen's Medical Centre, Nottingham University Hospital NHS Trust, Derby Road, NG7 2UH, United Kingdom

^b The Department of Obstetrics and Gynaecology, Faculty of Medicine, UKM Medical Centre, Kuala Lumpur, 56000, Malaysia

^c The Department of Obstetrics and Gynaecology, City Hospital, Hucknall Road, NG5 1PB, United Kingdom

^d Centre of Excellence for Autoimmunity in Cancer, School of Graduate Entry Medicine and Health, University of Nottingham, NG5 1PB, United Kingdom

^e Department of Histopathology, A Floor, East Block, Queen's Medical Centre, Nottingham University Hospital NHS Trust, United Kingdom

^f Centre for Analytical Bioscience, School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, United Kingdom

^g The School of Molecular Biology, Clinical Sciences Building, University of Nottingham, Hucknall Road, NG5 1PB, United Kingdom

HIGHLIGHTS

- Endometrial cancer (EC) risk in polycystic ovarian syndrome (PCOS) could be reduced by improving insulin resistance.
- Insulin sensitizers like metformin could help to reduce the risk of EC in PCOS.
- Understanding the molecular link between EC and PCOS in relation to hyperinsulinaemia is crucial.

ARTICLE INFO

Article history:

Received 23 August 2013

Accepted 22 October 2013

Available online 30 October 2013

Keywords:

Endometrial cancer

Endometrial hyperplasia

Metformin

PCOS

ABSTRACT

Current data indicate that there is a significant risk of endometrial cancer (EC) in women with polycystic ovarian syndrome (PCOS), although further research needed to clarify the exact molecular mechanisms. Endometrial hyperplasia is a premalignant condition that usually heralds EC and it shares identical risk factors with EC. Metabolic syndrome with a triad of obesity, hyperinsulinaemia and diabetes, which is commonly observed in PCOS appears to be a key mechanism in EC pathogenesis. Measures to improve insulin resistance could therefore play a role in reducing the risk of EC in women with PCOS. Metformin is an insulin sensitising agent which is safe, widely available and currently licensed for type-2 diabetes. It has been clearly shown in both animal and human studies that metformin is of value in reversing endometrial hyperplasia. Metformin may therefore prevent EC in PCOS. This article reviews the use of metformin in reducing EC risk in PCOS and makes a case for future research on this topic.

© 2013 Elsevier Inc. All rights reserved.

Contents

Introduction	249
Endometrial hyperplasia and endometrial cancer: the case for an alternative to progesterone treatment in PCOS	249
Endometrial cancer	249
Endometrial hyperplasia	249
Molecular links between PCOS and EC or EH, and the arguments in favour of a role for metformin in EC prevention in women with PCOS	250
Metformin (insulin sensitizer) in reducing EC risk in women with PCOS	250
Research published so far on reducing endometrial hyperplasia and endometrial cancer risk in PCOS using metformin (Table 1)	251
Conclusion and recommendations for future research	251
Authors' roles	251
Funding	251

* Corresponding author at: Department of Obstetrics and Gynaecology and Human Development, D Floor East Block, Queen's Medical Centre, University of Nottingham, NG7 2UH, United Kingdom.

E-mail address: mgxmsh@nottingham.ac.uk (M.N. Shafiee).

Conflict of interest	251
Acknowledgment	252
References	252

Introduction

Polycystic ovarian syndrome (PCOS) is a common, complex metabolic disorder affecting approximately 10% of women of reproductive age [1]. The widely accepted criterion for diagnosing PCOS is the Rotterdam, 2004 [2] criteria which requires that women with PCOS have two or more of the following in the absence of any other causes of chronic anovulation; clinical or biochemical evidence of hyperandrogenism, chronic oligo/anovulation and polycystic ovaries on ultrasound. PCOS is one of the commonest reasons women present with gynaecological problems, such as subfertility and abnormal menstrual cycles (oligomenorrhoea/amenorrhoea). Besides these, there are other health concerns related to PCOS which include obesity, cardiovascular disease, sleep apnoea, endometrial hyperplasia and endometrial cancer (EC). The prevalence of EC in women with PCOS varies depending on the criteria used to diagnose PCOS and the different subtypes of EC. It is estimated to be around 20–37% [3–5]. However, a recent systematic review revealed that the risk of EC was three times higher in women with PCOS compared to women without the disease [6]. The risk is even higher, up to three folds in obese women [7], and obesity is a predominant feature in PCOS. Management strategies to reduce the risk of EC in women with PCOS are therefore vital.

Current strategies to reduce EC risk in PCOS are aimed at ameliorating risk factors for EC in women with PCOS such as obesity, anovulation and endometrial hyperplasia (EH). Weight loss, the induction of regular menstrual withdrawal bleeding with progestogens in obese amenorrhoeic women with PCOS and the treatment of EH with oral progestogens, the levonorgestrel releasing intrauterine systems or a hysterectomy in PCOS women with atypical hyperplasia have therefore been the main stay of management. Progesterone hormones currently used to treat EH in women with PCOS are however associated with many side effects which make compliance a problem and they do not always work with a relapse rate of 14–30% [8]. An alternative treatment is therefore required. Metformin, a drug used in treating diabetes, which improves insulin resistance, has been shown in animal and some human studies to reverse EH. Metformin may therefore potentially prevent EC in PCOS through improved compliance and better cure rates of EH. Metformin may also help with weight loss as well as improve menstrual cyclicity further ameliorating the risk of EC in PCOS. This article examines the case for the use of metformin in reducing EC risk in PCOS. It begins by briefly outlining the epidemiology of EC and EH and the current challenges with managing EH in general. It then goes on to examine the molecular links between PCOS, EC and EH and the arguments in favour of a role for metformin in EC prevention in women with PCOS. Research published so far on EC risk reduction in PCOS using metformin is next presented and the review ends with some recommendations for future research.

Endometrial hyperplasia and endometrial cancer: the case for an alternative to progesterone treatment in PCOS

Endometrial cancer

A safe and effective way to prevent EC in women with PCOS is important because of the disease burden of EC and its economic costs. Globally, the incidence of endometrial cancer (EC) appears to be on a rising trend, especially with increasing obesity (a key issue in PCOS) rates [9]. It is projected to increase by 50% to 100% in the next 20 years [10,11]. Worldwide, EC comprises 4% of all cancers in

women and predominantly involves postmenopausal women [12]. In the United Kingdom, EC is the fourth most common cancer in women with 7,703 cases reported in 2008 and 10,000 women dying every year in Europe with this cancer [13]. The lifetime risk of developing EC is approximately 1 in 46 women in the United Kingdom. With regards to the economic burden of the treatment in early stage EC, the estimated cost was USD 13,199 to USD 14,040 per case, when the standard treatment protocol was practiced [10]. Moreover, in a report that used a simulation model, it is predicted that there would be about 13 million more obese people in the UK by the year 2030 and consequently more cases of cancers amongst other diseases. The cost estimation to treat obesity related diseases is also going to increase by approximately 1.9–2.0 billion pounds sterling per year in the UK [14].

The risk factors consistently linked to EC include family history, obesity, diabetes mellitus, nulliparity, tamoxifen use, estrogen therapy and polycystic ovarian syndrome (PCOS) [15]. A recent systematic review revealed that the risk of EC was three times higher in women with PCOS compared to women without the disease [6].

Endometrial hyperplasia

Endometrial hyperplasia (EH) which is a precancerous lesion of the endometrium has identical risk factors to EC and in one study, 30% of women with atypical EH who were treated hormonally progressed to cancer [16]. In addition, previous data has revealed that 40% and 59% of women who were diagnosed as EH and carcinoma-in-situ respectively, developed EC within 2 years when managed expectantly [17]. Concurrent EC was likely to occur in 20–43% [18]. These facts therefore strengthen the case for effective prevention of EC in women at high risk such as PCOS by treating EH in PCOS. In general the incidence of EH varies depending on the pathologic diagnosis with an incidence of 24–44% for simple hyperplasia and 25–38% for atypical hyperplasia [19,20].

The prevalence of EH in women with PCOS however varies from 1 to 48.8% [21–24]. In a study by Tingthanatikul et al., 2006 [21], the prevalence and clinical predictors of EH in amenorrhoeic women with anovulation were evaluated. Fifty-seven women were enrolled in the study of whom, 43 had PCOS and 14 had idiopathic anovulation. An endometrial biopsy was taken using a pipelle instrument. The results showed that the prevalence of EH was 48.8% and 35.7% in PCOS and idiopathic anovulatory women respectively. In another study [22], 56 women with PCOS presenting with infertility due to anovulation underwent both vaginal ultrasound assessments and endometrial biopsies. Thirty-six PCOS patients (64.3%) had proliferative endometrium and 20 (35.7%) had endometrial hyperplasia. Five of the latter (25%) had cytologic atypia.

These studies showing a high prevalence of PCOS however contrast with the results of two studies which suggest a lower prevalence of EH in PCOS [23,24]. In the first study, endometrial biopsies were obtained from 93 women with PCOS compared with 40 healthy women [23]. In women with PCOS, simple endometrial hyperplasia without atypia was found in one patient (1.08%). In the second study [24], a prevalence of EH of 1% was found in women with PCOS. In this study [24], 963 premenopausal women consecutively referred with the diagnoses PCOS and/or hirsutism during 1997–2008 to the Departments of Endocrinology and Gynaecology, Odense University Hospital, Denmark were recruited. In 2011, The Danish data bank of pathology was used to identify women with

Download English Version:

<https://daneshyari.com/en/article/3942835>

Download Persian Version:

<https://daneshyari.com/article/3942835>

[Daneshyari.com](https://daneshyari.com)