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Does free androgen index predict subsequent pregnancy outcome in women with recurrent miscarriage?

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BACKGROUND: Several studies have investigated plasma androgen levels in women with recurrent miscarriage (RM) with conflicting results on whether an association between hyperandrogenaemia and RM exists. However, none of these studies included sensitive androgen measurements using a large data set. We therefore investigated the free androgen index (FAI) in a large number of women with RM in order to ascertain whether hyperandrogenaemia is a predictor of subsequent pregnancy outcome. METHODS: We studied 571 women who attended the Recurrent Miscarriage Clinic in Sheffield and presented with ≥3 consecutive miscarriages. Serum levels of total testosterone and sex hormone-binding globulin were measured in the early follicular phase and FAI was then deduced. RESULTS: The prevalence of hyperandrogenaemia in RM was 11% and in a subsequent pregnancy, the miscarriage rate was significantly higher in the raised FAI group (miscarriage rates of 68% and 40% for FAI > 5 and FAI ≤ 5 respectively, $P = 0.002$). CONCLUSIONS: An elevated FAI appears to be a prognostic factor for a subsequent miscarriage in women with RM and is a more significant predictor of subsequent miscarriage than an advanced maternal age (≥40 years) or a high number (≥6) of previous miscarriages in this study.

Keywords: recurrent miscarriage; hyperandrogenaemia; polycystic ovary syndrome

Introduction

Recurrent miscarriage (RM) is defined as the loss of three or more consecutive pregnancies and affects ~1% of women (Stirrat, 1990). The aetiology of RM is thought to include chromosomal and uterine abnormalities, immunologic and endocrine factors, and infections (RCOG, 2003). An association between RM and polycystic ovary syndrome (PCOS) has been reported in many studies (Homburg *et al*., 1988; Sagle *et al*., 1988; Clifford *et al*., 1994), although the mechanism responsible for this association remains unclear. It was previously considered that hypersecretion of LH could be responsible (Regan *et al*., 1990), but more recent research suggests that this is unlikely (Li *et al*., 2000; Rai *et al*., 2000). Instead, hyperandrogenaemia, obesity and hyperinsulinaemia—all of which are associated with PCOS—have been identified as possible candidates (Tulppala *et al*., 1993; Okon *et al*., 1998; Wang *et al*., 2001; Glueck *et al*., 2002).

Several studies have investigated the androgen levels of women with RM with conflicting results on whether or not an association between hyperandrogenaemia and RM exists (Tulppala *et al*., 1993; Watson *et al*., 1993; Liddell *et al*., 1997; Okon *et al*., 1998; Bussen *et al*., 1999; Rai *et al*., 2000; Nardo *et al*., 2002). The apparent controversy is mainly attributed to the considerable variation in the specific androgens measured. However, in the assessment of hyperandrogenaemia, measurement of either free testosterone or the free androgen index (FAI) is now considered to be the most sensitive method (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Recommended methods for the measurement of free testosterone include equilibrium dialysis, calculation from total testosterone and sex hormone-binding globulin (SHBG), or ammonium sulphate precipitation, whereas direct assays for free testosterone were considered by the workshop to be of limited value. Of the previous studies, only two have included measurement of a sensitive marker for androgen excess (Tulppala *et al*., 1993; Okon *et al*., 1998). Secondly, the serum androgens should be measured in the early follicular phase (i.e. ≤day 7 of the cycle), whereas the majority of the previous studies included measurements later in the follicular phase. Thirdly, the majority of the studies presented data on only a small group of women ($n = 24–73$) and only two studies involved a large number of patients ($n = 344–2199$; Rai *et al*., 2000; Nardo *et al*., 2002). Crucially, there is not a single paper in the

literature which included sensitive androgen measurements in the correct phase of the cycle for a large number of women with RM.

In this study, we present FAI measurements from the early follicular phase using a large data set of women with RM. We aimed to deduce the prevalence of hyperandrogenaemia in RM and also to ascertain whether hyperandrogenaemia is a predictor of subsequent pregnancy outcome.

Materials and Methods

This study was conducted at the Recurrent Miscarriage Clinic of the Jessop Wing of the Royal Hallamshire Hospital, Sheffield, UK. A total of 571 women attended this clinic for the first time between January 1991 and December 2006 and presented with three or more consecutive miscarriages.

The patients in our study underwent investigations for RM following an established protocol (Li, 1998) which included chromosome analysis of both partners, testing for anticardiolipin antibodies and lupus anticoagulant, coagulation studies, pelvic ultrasonography, hysterosalpingogram and endocrinological investigations. Endocrinological investigations included serum measurements of Day 2–5 FSH, LH, estradiol, prolactin, testosterone, androstenedione, SHBG, thyroid function test and Day 21 progesterone.

Androgen measurements

For this study, we were interested in the serum total testosterone (T) and SHBG measurements. From 1991 until 2001, testosterone was measured using a coated tube radio-immunoassay (Coat-A-Count, Diagnostic Products Corporation) and from 2001 onwards, it was measured using an automated chemiluminescent immunoassay method (Advia Centaur, Bayer). From 1991 until 2000, SHBG was measured using a column 'saturation' method published by Iqbal and Johnson (1977) and from 2000 onwards, it was measured using an automated chemiluminescent immunoassay (Immulite analyser, Diagnostic Products Corporation). The intra- and inter-assay coefficients of variation, respectively, for the measurements were: T (1991–2001) 7.5%, 8.0%; T (2001 onwards) 6.2%, 4.4% and SHBG (2000 onwards) 6.8%, 9.4%. FAI was then calculated using $\text{FAI} = (\text{T}/\text{SHBG}) \times 100$.

A number of women had more than one measurement of FAI from different cycles and in the majority of these cases all measurements were found to be either consistently normal (FAI ≤ 5) or consistently high (FAI > 5). In these cases, we therefore took the average of these values. However, in a small number of cases, there were multiple FAI measurements, some of which were raised and some of which were normal. In these cases, we took the measurement nearest to the date of first attendance at the RM clinic, or an average of two measurements if both were within two menstrual cycles following the first clinic attendance.

Statistical analysis

Discrete variables were analysed using the χ^2 test. Normally distributed continuous variables were analysed using the Student's *t*-test; otherwise the Mann–Whitney *U*-test was used. Significance was assumed at $P < 0.05$.

Spearman's rank correlation coefficient was used to assess the correlation between the variables of FAI, age and body mass index (BMI). Logistic multiple regression analysis was used to analyse the various factors affecting subsequent pregnancy outcome.

Results

The mean ($\pm$SD) age of the women ($n = 571$) was 32.0 ($\pm$5.5) years. Three hundred and eighteen women (56%) had primary RM and the remaining 253 (44%) had secondary RM. The median (range) number of miscarriages prior to referral was 3 (3–15).

Of the 571 women attending the clinic, androgen measurements were available for 437 women. The FAI was found to be raised (FAI > 5) in 49 (11%) of cases.

Outcome of the first pregnancy after referral

Following referral to the RM clinic, we studied the outcome of the subsequent pregnancy for each of the 437 women for which androgen measurements were available. A total of 288 women had a subsequent pregnancy and of these 288 pregnancies, 114 (40%) resulted in a further miscarriage, 149 (52%) resulted in a live birth, 20 were of unknown outcome, 2 were ectopic pregnancies, 1 required termination of pregnancy and 2 were stillbirths. For the purpose of this paper, we studied only those outcomes of either miscarriage or live birth, giving a total of 263 pregnancies (from 263 women) for analysis (Fig. 1).

A study of these 263 pregnancies showed that the median (range) of the FAI for the pregnancies resulting in miscarriage was 2.4 (0.7–22.6) and the median (range) of the FAI for the pregnancies resulting in a live birth was 2.0 (0.6–12.7). Hence, the FAI was significantly higher in the miscarriage group ($P = 0.01$).

The outcomes of the subsequent pregnancy for patients with normal FAI (≤ 5) and for those with raised FAI (> 5) are given in Table I. We found that the post-referral rate of miscarriage was 40% in the normal FAI group, whereas it was significantly higher ($P = 0.002$) in the raised FAI group (68%).

We also further subdivided the FAI into three groups: (a) normal (FAI ≤ 5); (b) moderately elevated ($5 < \text{FAI} \leq 9$) and (c) significantly elevated (FAI > 9), and compared the pregnancy outcome after referral in each group (Table II). This demonstrated a significant trend of increasing miscarriage rate with increasing FAI ($P = 0.007$).

Endocrinological treatment

Of the 263 women whose pregnancies we have studied, 19 took clomifene citrate for anovulatory infertility in order to conceive their pregnancy, 5 women had ovarian drilling and 2 women had both clomifene and drilling. Hence, a total of 26 women had treatments prior to their subsequent pregnancy, of which 20 are in the normal FAI group (FAI ≤ 5) and 6 are in the raised FAI group (FAI > 5).

Patient demographics

The demographic details of the women with normal FAI and those with raised FAI are shown in Table III. We found no significant difference between the two groups in terms of the number of previous miscarriages or the proportion of women with a live birth prior to their referral. However, we did find

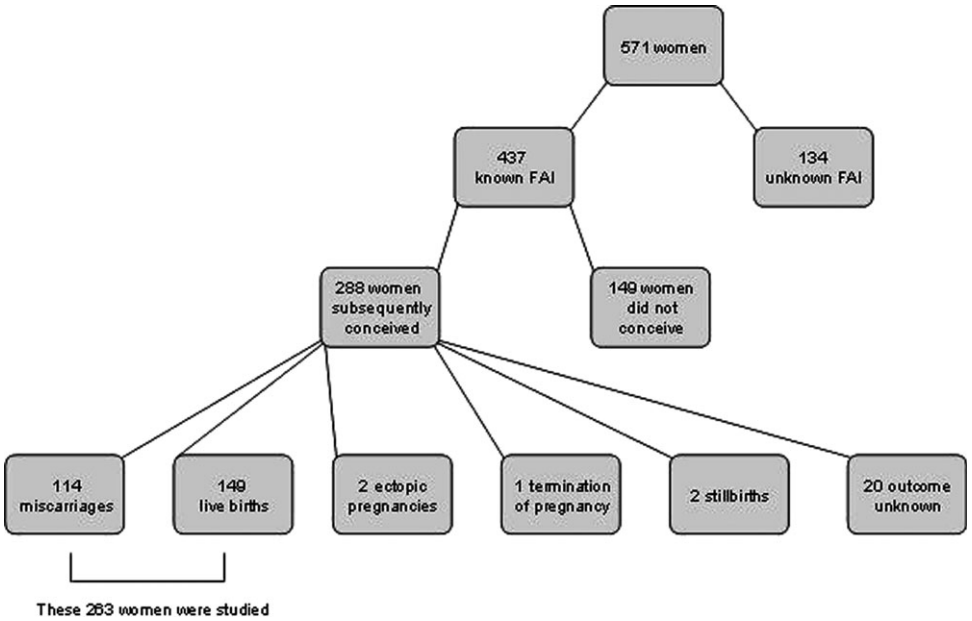

Figure 1: Flow diagram showing the final 263 pregnancies (from 263 women) used for analysis.

Table I. The outcome of the first pregnancy post-referral for patients with normal FAI (FAI $\leq$ 5) and with raised (FAI > 5).

FAI group	Pregnancy outcome		
	No. of miscarriages	No. of live births	Miscarriage rate (%)
FAI $\leq$ 5 (n = 229)	91	138	40
FAI > 5 (n = 34)	23	11	68

$\chi^2 = 9.4$; $P = 0.002$.

Table II. The outcome of the first pregnancy post-referral for patients with normal FAI (FAI $\leq$ 5), those with moderately elevated FAI (5 < FAI $\leq$ 9) and those with significantly elevated FAI (FAI > 9).

FAI group	Pregnancy outcome		
	No. of miscarriages	No. of live births	Miscarriage rate (%)
FAI $\leq$ 5 (n = 229)	91	138	40
5 < FAI $\leq$ 9 (n = 25)	16	9	64
FAI > 9 (n = 9)	7	2	78

$\chi^2 = 9.9$; $P = 0.007$.

that the women with raised FAI are significantly younger than those with a normal FAI ($P = 0.04$; $\rho = -0.137$) and that the women with raised FAI have a significantly higher BMI ($P < 0.001$; $\rho = +0.445$).

Factors affecting pregnancy outcome

Given the correlation between FAI and age and between FAI and BMI, we considered the possible impact of these and other demographic factors on the outcome of pregnancy (Table IV). We found that the FAI and the number of previous miscarriages were both significant in predicting the outcome of pregnancy but that the median BMI, mean age and a previous live birth were not significant factors in predicting outcome. However, the age does become a significant factor if the outcomes in different age groups are compared, using a cut-off of 40 years ($\geq$40 years compared with age < 40 years). The BMI remained an insignificant factor even when the outcomes

Table III. Characteristics of the women with RM in the normal FAI and raised FAI groups.

	Women with FAI$\leq$5 (n = 388)	Women with FAI>5 (n = 49)	P
No. of previous miscarriages	3.0 (3–14)	3.0 (3–9)	NS
Previous live birth			
Yes	163	22	NS
No	225	27	
Age (years)	32.3 [$\pm$5.3]	30.5 [$\pm$5.6]	0.04
BMI (kg/m^2)	24.0 (16–47)	29.7 (20–45)	<0.001

Values are given as n, median (ranges) or mean [$\pm$SD].
BMI = body mass index; NS = not significant, i.e. $P > 0.05$.

Table IV. Characteristics of the women with RM and their effect on the pregnancy outcome.

	Miscarriage (n = 114)	Live birth (n = 149)	P
FAI	2.4 (0.7–22.6)	2.0 (0.6–12.7)	0.01
No. of previous miscarriages	3.0 (3–9)	3.0 (3–6)	<0.05
Previous live birth			
Yes	45	63	NS
No	69	86	
Age (years)	31.7 [$\pm$5.4]	31.3 [$\pm$4.7]	NS
BMI (kg/m^2)	24.6 (18–41)	24.2 (19–44)	NS

Values are given as n, median (ranges) or mean [$\pm$SD].

in different BMI groups were compared (BMI $\geq 30\ kg/m^2$ compared with BMI $< 30\ kg/m^2$). Using logistic multiple regression analysis, the three most important factors in predicting a subsequent miscarriage (in decreasing order of importance) are a raised FAI (>5), an age >40 years and having previously had at least six miscarriages.

Discussion

In this study, we present measurements of the FAI, a sensitive marker for androgen excess, taken in the early follicular phase from a large group of women with RM. We found that the prevalence of hyperandrogenaemia in RM is 11% and that a raised FAI (FAI > 5) is associated with a significantly increased risk of a further miscarriage in a subsequent pregnancy. Furthermore, we have clearly demonstrated a trend of an increasing risk of miscarriage with increasing FAI.

The prevalence of hyperandrogenaemia in RM determined in this study (FAI > 5 in 11% of cases) is in broad agreement with the results of the three previous smaller ($n < 89$) studies which investigated this prevalence using measurements of either free testosterone or FAI (13–20%; Tulppala *et al.*, 1993; Okon *et al.*, 1998; Li *et al.*, 2000).

Our results in this paper can be compared with the only two previous studies in the literature which used a sensitive marker for androgen excess in order to study the androgen levels in women with RM (Tulppala *et al.*, 1993; Okon *et al.*, 1998). Although both studies were only small ($n \leq 50$), they both suggested an association between hyperandrogenaemia and RM which our larger study now confirms.

Our results can also be compared with the only two large-scale studies which investigated the androgen levels in women with RM (Rai *et al.*, 2000; Nardo *et al.*, 2002). Both studies used serum total testosterone levels only, which has since been noted as a potentially less sensitive method of detecting androgen excess (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Indeed, when we used total testosterone as the measurement to assess androgen excess in our data set (following the method of Rai *et al.*, 2000 and Nardo *et al.*, 2002), we did not find this measurement had any prognostic value.

The trend of an increased risk of miscarriage with increasing FAI shows that the risk of a subsequent miscarriage is nearly doubled across the extent of the range studied (78% for FAI > 9; 40% for FAI ≤ 5). However, a degree of caution is required in the interpretation of this trend since, although the differences are highly statistically significant ($P = 0.007$), only a small number of pregnancies ($n = 9$) occurred in women with significantly elevated values of FAI (FAI > 9).

There are three possible criticisms of this study. The first is that over the time period of the study, two different methods have been used to measure the testosterone and SHBG. This is unfortunately an inevitable consequence of a study which has been conducted over a long time period, during which time laboratory techniques will have changed. Although there are no data available to assess the comparability of the different methods, we found no significant difference ($P = 0.9$) in the proportion of women with raised FAI whichever method was used, thus indicating that any difference between the measurements is not sufficient to significantly affect our results.

The second possible criticism is that the androgen measurements were usually made when the woman first attended the RM clinic and not at the time of her subsequent pregnancy. However, most patients who conceived did so within 6 months of referral, during which time it is unlikely that the androgen levels will have varied significantly.

The third possible criticism is that 26 women in the study had endocrinological treatments (19 took clomifene citrate, 5 had ovarian drilling, 2 had both) prior to their subsequent pregnancy, which may have affected or lowered the androgen levels between measurement and conception. This possibility does not affect the 20 women grouped in the normal FAI group (FAI ≤ 5) but could affect the six women who are grouped in the raised FAI group (FAI > 5). We do not feel it is necessary to exclude these women since insufficient information is available on the extent to which these treatments may lower the androgen levels. Furthermore, four of these women have an FAI > 9 and it is therefore unlikely that their androgen levels will have been lowered to a level of FAI ≤ 5. However, if we did exclude the six women with raised FAI who received treatment prior to their subsequent pregnancy, there is still a statistically significant difference ($P = 0.03$) between the miscarriage rate in the normal and raised FAI groups.

Confounding factors

Table III shows the characteristics of the women with normal FAI and those with raised FAI and demonstrates that there is no significant difference between the two groups in terms of the total number of previous miscarriages or the proportion of women with a live birth prior to their referral. However, it does show that the women with raised FAI were significantly younger and had a significantly higher BMI. We therefore investigated the impact of these and other demographic factors on the outcome of pregnancy (Table IV).

The negative correlation between FAI and age shown here is in good agreement with previous studies which have demonstrated a decline in the secretion of ovarian androgens with age (Piltonen *et al.*, 2003, 2004). Previous studies have clearly demonstrated that advancing maternal age (≥40 years) is a predictor of adverse pregnancy outcome (Clifford *et al.*, 1997). In this study, we found that the mean age itself is not a significant predictor of miscarriage, probably because the group as a whole are relatively young with only a small proportion (5%) ≥40 years. However, once we compared the pregnancy outcome at age ≥40 years with the outcome in younger women (<40 years), the difference did become significant. Nevertheless, logistic multiple regression analysis in our population revealed the somewhat surprising result that a raised FAI (>5) is actually a more important predictor of a subsequent miscarriage than a maternal age ≥40 years. In any case, the age–FAI association cannot be contributing to the FAI–miscarriage association because here we have an increased miscarriage rate with raised FAI where the women are *younger*.

The positive correlation between FAI and BMI is not surprising and can be explained by decreased hepatic production of SHBG secondary to increased insulin levels associated with

increased BMI (Metwally *et al*., 2007). In this study, we have shown that the BMI is not a significant predictor of miscarriage, even when the outcomes in different BMI groups were compared (BMI $\geq 30\ kg/m^2$ compared with BMI $< 30\ kg/m^2$). However, the significance of more severe levels of obesity (BMI $\geq 35\ kg/m^2$) cannot be assessed in this study due to small patient numbers and therefore further studies are required to assess the impact of more significant degrees of obesity on RM.

In agreement with previous results (Clifford *et al*., 1997), a previous live birth is not a significant predictor of subsequent pregnancy outcome, but the number of previous miscarriages is important, especially as this becomes high ($\geq$6). However, a high number of previous miscarriages ($\geq$6) is again not as important a predictor of subsequent miscarriage as a raised FAI.

In this study, we have looked specifically at the effect of FAI on pregnancy outcome, but it is important to note that hyperandrogenaemia is often associated with other metabolic disturbances such as hyperinsulinaemia or elevated levels of plasminogen activator inhibitor-1. Since this is a retrospective study, it has not been possible to include the measurement of such parameters but, having demonstrated that an elevated FAI is an important marker for a subsequent miscarriage, further studies are now required to establish if other metabolic disturbances associated with hyperandrogenaemia could be responsible.

Mechanisms of miscarriage in women with elevated FAI

Possible mechanisms for the association between hyperandrogenaemia and RM include an adverse impact of hyperandrogenaemia on endometrial development (Okon *et al*., 1998; Watson *et al*., 1998; Tuckerman *et al*., 2000), a detrimental effect on oocyte quality and hence embryo viability (van Wely *et al*. 2005) or an indirect effect via the insulin pathway, perhaps via the insulin-like growth factor pathway (Tulppala *et al*., 1993; Okon *et al*., 1998).

Summary

RM is a heterogeneous condition with a wide variety of recognized aetiologies. In this study, we have focused on one specific factor, hyperandrogenaemia, by conducting the first large-scale study of plasma androgen levels in women with RM using the FAI as a sensitive marker for androgen excess. We found that the prevalence of hyperandrogenaemia (FAI $>$ 5) in RM is 11% and that in this group of women, there is a significantly increased risk of miscarriage in a subsequent pregnancy. Furthermore, in our population, the importance of a raised FAI ($>$5) ranks as a more significant predictor of a subsequent miscarriage than an advanced maternal age ($\geq$40 years) or a high number ($\geq$6) of previous miscarriages.

We recognize that not all investigators currently measure testosterone and SHBG in order to deduce FAI, which may in part be because of a lack of good commercial assays available. However, we hope that with technological advancement in this area, more investigators will routinely measure FAI and therefore provide further data on what we believe to be a very important area. In addition, it will be of interest to investigate whether therapeutic intervention to reduce the FAI improves the outcome in this group of women.

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