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Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo

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Objective To study the significance of breast size increment in pregnancy, and the impact of metformin during pregnancy on breastfeeding in women with polycystic ovary syndrome (PCOS).

Design A follow-up study of a randomised controlled trial (the PregMet study).

Setting Eleven secondary care centres.

Population Women with PCOS during pregnancy and postpartum.

Methods Women with PCOS were randomised to treatment with metformin or placebo from the first trimester to delivery. Questionnaires were sent to 240 participants 1 year postpartum: 186 responded.

Main outcome measures Pre-pregnancy and late-pregnancy brassiere size and breastfeeding patterns were registered, and androgen levels were measured in the mothers.

Results No difference in breast size increment and breastfeeding were found between the placebo and metformin groups. Breast size increment correlated positively with the duration of both exclusive and partial breastfeeding, whereas body mass index (BMI) correlated negatively with the duration of partial breastfeeding. Dehydroepiandrostenedione-sulphate (DHEAS), testosterone and free testosterone index (FTI) in pregnancy did not correlate with breast size increment or duration of breastfeeding. Women with no change in breast size were more obese, had higher blood pressure, serum triglycerides and fasting insulin levels, and had a shorter duration of breastfeeding compared with those with breast size increment.

Conclusions Metformin and androgens had no impact on breastfeeding. Women with PCOS who had no breast size increment in pregnancy seem to be more metabolically disturbed and less able to breastfeed.

Keywords Androgens, breast size increment, breastfeeding, metformin, polycystic ovary syndrome, pregnancy.

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Introduction

Polycystic ovary syndrome (PCOS) is a common condition, and is associated with reduced fertility; however, most women with PCOS become pregnant and give birth.[1,2] Except for one case report and one pilot study,[3,4] little has been reported about PCOS and breastfeeding. For years, the clinical impression has been that fewer women with PCOS were breastfeeding, and in a small pilot study we found support for this observation.[4] After performing a larger randomised controlled trial (RCT) on metformin versus placebo in pregnant women with PCOS,[5] we thought it important to investigate whether treatment with metformin in pregnancy could have any impact on breastfeeding.

A large number of observational studies have been published about the possible health effects of breastfeeding, both for the mother and the child.[6–8] In particular the positive effects of breast milk on the incidence of childhood obesity and diabetes have been stressed.[9] Factors or reasons for breastfeeding or not breastfeeding have mostly been attributed to maternal age and education level, socioeconomic situation and smoking habits.[10] Lately, obesity has been associated with a low breastfeeding rate.[11–14] The metabolic and hormonal determinants for the ability to breastfeed have not yet been studied to a great extent. As there seems to be a large proportion of women with PCOS struggling with and failing to breastfeed, the question emerged: what makes some women breastfeed easily and others not? Which clinical, metabolic or hormonal factors can be linked or associated with the ability to breastfeed?

Based on clinical observations and a former pilot study,[15] we hypothesised that: (1) metformin in pregnancy would not affect breastfeeding; (2) breast size increment during pregnancy is important for successful breastfeeding; (3) high maternal androgen levels would have a negative impact on breastfeeding.[4,16]

Study design

The present study is a follow-up of the 'Metformin treatment in pregnant PCOS women' (PregMet) study, which was a prospective, randomised, double-blind, multicentre trial, comparing 2000 mg of metformin daily against placebo from the first trimester to delivery.[5] In short, the inclusion criteria were: (1) PCOS diagnosed according to the Rotterdam criteria;[17] (2) age 18–45 years; (3) gestational age between 5 and 12 weeks; and (4) a singleton viable fetus shown on ultrasonography. The exclusion criteria were: alanine aminotransferase (ALAT) > 90 iu/l; serum creatinine concentration > 130 μmol/l; known alcohol abuse; previously diagnosed diabetes mellitus or fasting serum glucose > 7.0 mmol/l at the time point of inclusion; treatment with oral glucocorticoids; or use of drugs known to interfere with metformin.

Two hundred and seventy-four pregnancies (in 258 women) were randomly assigned to treatment with either metformin or placebo (16 women participated twice). In one patient a partial 21-hydroxylase deficiency had been overlooked, but she was excluded after randomisation. Randomisation, blinding and the measurements performed are described in detail elsewhere.[5] All participants received written and individual verbal counselling on diet and lifestyle at inclusion. Thereafter treatment with 500 mg of metformin (metformin hydrochloride, Metformin®; Weifa AS, Oslo, Norway) or identically coated placebo tablets was initiated. The participants were instructed to take one tablet twice daily during the first week and two tablets twice daily for the rest of the study period, i.e. until delivery. Study medication was stopped upon delivery. To counteract a possible adverse effect of metformin on vitamin B levels, patients were advised to take 0.8 mg of folic acid daily, and one daily multivitamin tablet containing both vitamins B_6 and B_{12}.

Standardised interviewer-administered questionnaires were used to obtain self-reported data on former medical and gynaecologic/obstetric history, ethnicity, employment, smoking habits, study medication and concomitant medication. Biometric variables, including height, weight, blood pressure and heart rate, were recorded at inclusion and at each pre-scheduled visit at gestational weeks 19, 24, 32 and 36. Fasting blood samples were directly analysed at each study centre for plasma glucose. A 75-g oral glucose tolerance test (OGTT) was performed at inclusion, and at gestational weeks 19 and 32, according to the World Health Organization (1998) recommendations.[18,19] Venous blood samples were drawn from an antecubital vein between 08:00 and 11:00 hour, after an overnight fast. Blood pressure and heart rate were measured while the patient was in the sitting position after at least 10 minutes of comfortable rest in a chair. The blood pressure was measured three times, 2 minutes apart, with digital devices. The mean of the second and third measurements was calculated. Body weight was recorded with light clothes on and without shoes. Gestational age was determined by mid-pregnancy ultrasound examination, measuring bi-parietal diameter, femur length and mean abdominal diameter of the fetus.

The follow-up study

The participants in the PregMet study gave their written consent to be contacted after the end of the original study. Out of the 274 pregnancies included in the PregMet study, three patients had miscarriages, 12 dropped out, one was excluded because of misdiagnosis and two babies died perinatally. Sixteen women participated twice. Only their first participation was included in the follow-up study. Two hundred and forty women were invited to participate in the follow-up study. One year after delivery a questionnaire and prepaid envelope was sent by mail. A reminder was sent about 2–3 weeks later to the non-responders. At this time point the participants were not aware of whether they had been randomised to metformin or to placebo.

The participants were asked about the length of exclusive breastfeeding (in months) and at what point in time they stopped breastfeeding. We asked about bra size before pregnancy and bra size at the end of pregnancy. Bra sizes were recorded in the following manner: A = 1; B = 2; C = 3; D = 4; E = 5. Bra chest circumferences were recorded as: 70, 75, 80, 85, 90, 95 or 100 cm. An increase from 70 to 75 cm also results in an increase of one cup size. If a woman had 80B in early pregnancy and 85C at

delivery, this implies an increase of two bra cup sizes (from B to C = 1 and from 80 to 85 = 1).

Data management

All data entry, data management and data analyses were performed at the Institute of Laboratory Medicine, Children's and Women's, Norwegian University of Science and Technology. Questionnaires were sent out successively 1 year postpartum.

Statistical analysis

The data are analysed according to the intention-to-treat principle using PASW STATISTICS 18.0 for WINDOWS (SPSS Inc., Chicago, USA). The differences between the study groups were compared with two-tailed *t*-tests for independent samples. Where normality could not be assumed, the Mann–Whitney *U*-test was used. Fisher's exact test was used for the evaluation of discrete data. Values are reported as means (SDs) or absolute numbers. A two-tailed $P < 0.05$ was considered significant. A χ^2 test was used to test differences between the groups. If the smallest expected value in a cell was less than five, we used Fisher's exact test. Associations were investigated with univariate and multivariate linear regression analyses. Two-tailed tests were used throughout. No adjustments for multiple testing were performed.

Results

One hundred and eighty-six women with PCOS out of 240 who participated in the PregMet study responded to the questionnaire at 1 year postpartum. No differences were found in baseline data between those who were randomised to the metformin and the placebo groups during pregnancy (Table 1).

Metformin effect on breastfeeding

There were no differences in the duration of exclusive breastfeeding or the duration of partial breastfeeding between mothers with PCOS treated with metformin and those treated with placebo (Table 2).

Breast size and breastfeeding

There were no differences in breast size before pregnancy or breast size increment during pregnancy between the metformin and the placebo groups (Table 2). The increase in breast size was unrelated to maternal body mass index (BMI) or change in BMI (data not shown).

The duration of both exclusive and partial breastfeeding correlated positively with breast size increment in pregnancy in both univariate and multivariate regression analyses (Table 3). Furthermore, increased BMI was related to a shorter duration of partial breastfeeding. When the infants were 3 months old, 26 women had stopped breastfeeding. No or inadequate milk production was given as the reason in 24 cases. Maternal dehydroepiandrostenedione-sulphate (DHEAS), testosterone and free testosterone index (FTI) in late pregnancy had no impact on breast size increment or duration of breastfeeding (Table 3).

Effect of breast size increment during pregnancy

When we dichotomised women into those who reported an increase in bra size during pregnancy and those who did not, women with no breast size increment had higher blood pressure, were more obese, had higher fasting insulin and triglyceride levels already at inclusion in the first trimester of pregnancy, compared with those who experienced breast size increment (Table 4). Also, at the end of pregnancy, women with no breast size increment were more obese, but had gained less weight during pregnancy. Weight gain in pregnancy did not correlate with breast size increment, when adjusted to baseline BMI. After delivery, women with no breast size increment had a shorter period of exclusive and partial breastfeeding (Table 4).

Discussion

The most important findings of the present study are: (1) that neither metformin nor androgens had any impact on breast size increment in pregnancy or breastfeeding; and (2) women with PCOS who do not have breast size increment during pregnancy seem to be more metabolically deranged and breastfeed less than those with breast size increment.

The frequency of breastfeeding is high in the Norwegian population. It is a part of a targeted health policy, and is encouraged and facilitated by authorities through maternity out-patient clinics, paid maternity leave and information campaigns. There is a general opinion supported by health authorities that breastfeeding is beneficial both for the mother and the baby, and that all women who can breastfeed should do so. This is clearly reflected in the present study by the high frequency and long duration of breastfeeding.

Androgens such as testosterone inhibit lactation, and in the era before dopamine agonists, testosterone alone, or in combination with estrogens, was used to inhibit lactation.[20,21] In our pilot study we found that the pre-androgen DHEAS showed a weak negative correlation with breastfeeding in women who have PCOS.[4] In a random sample of women, mid-pregnancy androgen levels correlated negatively with breastfeeding.[16] Therefore, we hypothesised that elevated levels of androgens interferes with lactation. In the present study mean androgen levels were high in the first trimester in women with PCOS, suggesting

Table 1. Maternal characteristics in the first trimester (baseline data) and at the end of pregnancy according to treatment allocation in pregnancy

	n	Metformin	*n*	Placebo	*P*
First trimester					
Age (years)	98	29.7 ± 4.4	88	29.1 ± 4.3	0.38
BMI (kg/m^2)	98	29.3 ± 7.1	88	27.4 ± 6.0	0.11***
Systolic blood pressure (mmHg)	98	119 ± 12	88	116 ± 11	0.90***
Diastolic blood pressure (mmHg)	98	72 ± 9	88	71 ± 9	0.37***
Fasting glucose (mmol/l)	98	4.6 ± 0.5	88	4.6 ± 0.6	0.68
2-hour glucose (mmol/l)	97	5.7 ± 1.6	87	5.7 ± 1.6	0.98
Insulin (pmol/l)	96	109 ± 79	85	101 ± 80	0.53
Testosterone (nmol/l)	96	4.3 ± 1.9	85	4.2 ± 2.0	0.91
DHEAS (μmol/l)	96	4.8 ± 2.1	85	4.7 ± 2.1	0.74
FTI	96	0.24 ± 0.11	86	0.23 ± 0.14	0.40
Smoking no. (%)	98	9 (10)	88	3 (3)	0.14*
Single/married or cohabiting	95	5/90	87	0/87	0.06 *
Education (≤12 years/>12 years)	95	29/66	86	32/54	0.34
End of pregnancy					
BMI (kg/m^2)	93	32.5 ± 7.0	78	31.3 ± 5.5	0.19***
BMI gain in pregnancy (kg/m^2)	93	3.0 ± 2.8	78	3.8 ± 1.7	0.25***
Systolic blood pressure (mmHg)**	97	121 ± 13	88	117 ± 12	0.04***
Diastolic blood pressure (mmHg)**	98	76 ± 9	88	74 ± 10	0.54***
Fasting glucose (mmol/l)**	88	4.4 ± 0.7	70	4.4 ± 0.5	0.96
Fasting insulin (pmol/l)**	97	139 ± 77	88	157 ± 109	0.19
Testosterone (nmol/l)**	97	5.3 ± 2.5	88	6.2 ± 5.3	0.15
DHEAS (μmol/l)**	97	3.3 ± 1.6	94	2.7 ± 1.2	0.007
FTI**	96	0.15 ± 0.09	88	0.17 ± 0.14	0.40
Smoking no. (%)**	98	5 (5)	86	2 (2)	0.45

*Fischer's exact test.
**Last measured or registered in pregnancy: i.e. for those who passed gestational week 36 it was gestational week 36, for those who gave birth after gestational week 24 but before gestational week 36 it was the last visit before birth.
***Mann–Whitney *U*-test.

Table 2. Breast size and breast feeding in women with PCOS according to treatment allocation

	n	Metformin	*n*	Placebo	*P*
Pre-pregnancy bra cup size (no.)	97	3.1 ± 1.2	86	3.0 ± 1.3	0.93
Pre-pregnancy bra chest circumference (cm)	97	83.0 ± 7.7	86	81.5 ± 7.1	0.15
Late pregnancy bra cup size (no.)	96	3.7 ± 1.2	85	3.7 ± 1.3	0.87
Late pregnancy bra chest circumference (cm)	97	84.8 ± 7.1	86	83.8 ± 7.2	0.38
Change in bra cup size (no.)	97	0.7 ± 0.7	86	0.7 ± 0.7	0.80
Change in chest circumference (no.)	97	0.3 ± 0.6	86	0.5 ± 0.7	0.16
Total bra cup change in pregnancy (no.)	97	1.1 ± 1.0	87	1.2 ± 1.1	0.77
Exclusive breast feeding (months)	98	4.5 ± 2.8	88	3.9 ± 2.9	0.08*
Any breast feeding (months)	98	8.8 ± 3.9	88	8.5 ± 4.0	0.59*

Bra cup sizes: A = 1; B = 2; C = 3; D = 4; E = 5.
Bra chest circumferences: 70, 75, 80, 85, 90, 95 and 100 cm (an increase from 70 to 75 cm results in an increase of one cup size).
If a woman had a bra size of 80B in early pregnancy and 85C at delivery, this would indicate an increase of two sizes in the total bra cup size.
*Mann–Whitney *U*-test.

that metabolic derangement is already present at this stage. Although we found no negative impact of DHEAS or FTI on breastfeeding, obesity, higher blood pressure, high serum triglycerides and high fasting insulin levels correlated negatively with breastfeeding, suggesting an association with metabolic function.

There is an old notion among nursing counsellors that mothers without 'milk pain' or a certain degree of breast

Table 3. The duration of breastfeeding in univariate and multivariate regression analyses

	Univariate			Multivariate		
	B	95% CI	*P*	*B*	95% CI	*P*
Exclusively breast feeding (months)						
Maternal age (years)	−0.02	(−0.12; 0.07)	0.66	0.01	(−0.10; 0.12)	0.91
Maternal BMI (kg/m^2)*	−0.07	(−0.14; 0.01)	0.03	−0.03	(−0.10; 0.04)	0.42
Education (≤12 years = 1; >12 years = 2)	0.54	(−0.40; 1.35)	0.29	0.26	(−0.73; 1.26)	0.60
FTI*	−2.89	(−6.43; 0.65)	0.11	−2.68	(−6.34; 0.99)	0.15
DHEAS (μmol/l)*	0.03	(−0.26; 0.31)	0.86	0.13	(−0.17; 0.44)	0.39
Total change in bra cup size in pregnancy (no.)	0.77	(0.38; 1.15)	<0.001	0.73	(0.28; 1.18)	0.002
Smoking (no = 1; yes = 2)*	0.39	(−1.78; −2.56)	0.72	−0.25	(−2.79; 2.29)	0.85
Fetal birthweight (g)	0.00	(−0.00; 0.00)	0.53	0.00	(−0.00; 0.00)	0.48
Fetal gestational age (days)	−0.00	(−0.03; 0.03)	0.99	0.02	(−0.03; 0.07)	0.43
Randomisation (metformin = 1; placebo = 2)	−0.61	(−1.43; 0.121)	0.15	−0.53	(−1.41; 0.35)	0.24
Any breastfeeding (months)						
Maternal age (years)	−0.06	(−0.19; 0.07)	0.34	−0.04	(−0.18; 0.11)	0.60
Maternal BMI (kg/m^2)	−0.19	(−0.28; −0.11)	<0.001	−0.14	(−0.23; −0.04)	0.007
Education (≤12 years = 1; >12 years = 2)	1.72	(0.52; 2.91)	0.005	1.14	(−0.17; 2.45)	0.09
FTI*	−3.85	(−8.72; 1.02)	0.12	−3.17	(−7.99; 1.65)	0.20
DHEAS (μmol/l)*	−0.07	(−0.46; 0.33)	0.72	0.17	(−0.23; 0.58)	0.40
Total change in bra cup size in pregnancy (no.)	0.90	(0.35; 1.43)	0.001	0.87	(0.17; 1.46)	0.005
Smoking (no = 1; yes = 2)*	1.14	(−1.82; 4.82)	0.45	−1.17	(−4.51; 2.17)	0.49
Fetal birthweight (g)	0.00	(−0.00; 0.00)	0.34	−0.00	(−0.00; 0.00)	0.24
Fetal gestational age (days)	0.01	(−0.04; 0.05)	0.82	0.00	(−0.07; 0.07)	0.93
Randomisation (metformin = 1; placebo = 2)	−0.31	(−1.45; 0.82)	0.59	−0.18	(−1.34; 0.99)	0.77

*Last measured or registered in pregnancy: i.e. for those who passed gestational week 36 it was gestational week 36, and for those who gave birth after gestational week 24 but before gestational week 36 it was the last visit before birth.

tension have difficulties in breastfeeding. We are, however, not aware of any studies that have explored the correlation between breast size increment and breastfeeding. We evaluated breast size increment simply by asking about increases in bra size during pregnancy. An increase in bra size correlates positively with the duration of exclusive and partial breastfeeding. When adjusting for variables known to correlate with or influence breastfeeding in a multivariate regression model, we find that breast size increment still correlates positively with both exclusive and partial breastfeeding. This has not been reported before, and confirms clinical observations. The reason given for not breastfeeding at 3 months postpartum was shortage of milk in 86% of cases, not lack of motivation.

Interestingly, in comparing women with PCOS who experience breast size increment or not during pregnancy, we find metabolic differences between the groups. Those with no breast size increment have higher blood pressure, and higher fasting insulin and triglyceride levels in early pregnancy. They are more obese in both early and late pregnancy. Both the exclusive and the partial breastfeeding periods are shorter compared with those with breast size increment.

Some, but not all, epidemiological studies indicate that breast milk protects the offspring from obesity and diabetes.[22–24] Our results might be open for a different understanding or interpretation. Underlying metabolic and/or endocrine factor(s) may be a common trait that both promote breast size increment and facilitate the ability to breastfeed. As mothers with no breast size increment, resulting in no or just a short period of breastfeeding, are more obese and have higher insulin levels, their offspring may be more prone to develop obesity and diabetes, independent of breast milk. A recent retrospective study reports on more android obesity, more insulin resistance, and higher blood pressure and cholesterol levels 16–20 years after the last pregnancy in women who had a shorter duration of breastfeeding.[25] The authors conclude that brief breastfeeding induces weight retention and fat mass accumulation, resulting in increased risk of cardiometabolic disorders in later life. These findings support ours, although we interpret them differently: women who are not able to breastfeed are metabolically inferior compared with those who breastfeed easily.

The weakness of the study is the self-reported bra size. Not all women wear the correct sized bra, and there might be some differences in size between different brands. There is a possibility that women who actually increased in breast size during pregnancy did not shift for a larger bra size. All

Table 4. Patient characteristics according to breast size increment in pregnancy

	n	No increase in bra size	*n*	Increase in bra size	*P*
In the first trimester of pregnancy					
Age (years)	59	30.1 ± 4.0	125	29.1 ± 4.5	0.07**
BMI (kg/m^2)	59	30.6 ± 6.8	125	27.2 ± 6.2	0.001**
Systolic blood pressure (mmHg)	59	121 ± 11	125	116 ± 12	0.004**
Diastolic blood pressure (mmHg)	59	74 ± 10	125	71 ± 8	0.10**
Fasting glucose (mmol/l)	59	4.6 ± 0.5	125	4.6 ± 0.5	0.67
2-hour glucose (mmol/l)	59	5.8 ± 1.7	124	5.5 ± 1.5	0.24
Fasting insulin (pmol/l)	59	133 ± 119	120	92 ± 44	0.01
Total cholesterol (mmol/l)	59	4.65 ± 0.89	124	4.64 ± 0.96	0.94
HDL cholesterol (mmol/l)	59	1.61 ± 0.38	125	1.63 ± 0.37	0.79
Triglycerides (mmol/l)	59	1.36 ± 0.78	125	1.13 ± 0.54	0.05
Testosterone (nmol/l)	59	4.3 ± 2.3	120	4.3 ± 1.7	0.90
FTI	59	0.24 ± 0.15	120	0.23 ± 0.12	0.72
Smoking no. (%)	59	4 (6)	131	9 (7)	1.0***
At the end of pregnancy*					
BMI (kg/m^2)	56	33.9 ± 6.0	114	31.2 ± 7.3	0.001**
BMI gain in pregnancy (kg/m^2)	56	2.8 ± 1.8	114	4.0 ± 4.3	0.003**
Systolic blood pressure (mmHg)	58	120 ± 12	125	118 ± 14	0.16**
Diastolic blood pressure (mmHg)	58	77 ± 10	125	75 ± 10	0.13**
Fasting glucose (mmol/l)	52	4.4 ± 0.4	105	4.4 ± 0.7	0.97
Fasting insulin (pmol/l)	59	152 ± 75	131	146 ± 102	0.65
Total cholesterol (mmol/l)	58	6.70 ± 1.20	125	6.70 ± 1.30	0.99
HDL cholesterol (mmol/l)	58	1.89 ± 0.44	125	1.81 ± 0.40	0.25
Triglycerides (mmol/l)	56	2.93 ± 1.20	125	2.79 ± 1.03	0.47
Testosterone (nmol/l)	58	5.9 ± 5.2	125	5.6 ± 3.5	0.71
FTI	58	0.16 ± 0.15	125	0.16 ± 0.10	0.82
Smoking no. (%)	59	1 (2)	123	6 (5)	0.44***
Postpartum					
Exclusive breastfeeding (months)	59	3.4 ± 2.9	125	4.7 ± 2.7	0.006**
Any breastfeeding (months)	59	7.3 ± 4.5	125	9.3 ± 3.4	0.006**
Smoking no. (%)	59	5 (8)	123	15 (12)	0.61***

*Last measured in pregnancy, i.e. most often at gestational week 36. For those who gave birth before 36 weeks of gestation, it is measured at the last visit before delivery.
**Mann–Whitney *U*-test.
***Fischer's exact test.

in all bra size is a crude measurement, but it is three-dimensional and we believe that women in general do remember the size of their bra, as they have to ask or look for it when shopping. If they don't remember the size, they can check the tag on the bra.

The fact that women who reported no increase in bra size did not represent a random group is reflected by our findings that they were more obese, and had higher blood pressure, serum triglycerides and fasting insulin levels. Finding this difference with a crude measurement indicates that the significance would probably be more pronounced using a more accurate tool.

In conclusion, metformin and androgens had no impact on breastfeeding. Pregnant women with PCOS with no breast size increment seem to be more metabolically disturbed, and are less able to breastfeed.

Disclosure of interests

The authors have nothing to disclose.

Contribution to authorship

EV made substantial contributions to the conception and design of the study, to the analysis and interpretation of data, and to writing the article, and gave final approval of the version to be published. JN contributed to the design of the study, collected and analysed data, and revised and gave final approval of the data to be published. HL contributed to the design of the study, collected and analysed data, and revised and gave final approval of the data to be published. AH-H contributed to the design of the study, collected and analysed data, and revised and gave final approval of the data to be published. MM analysed and interpreted the data, drafted the article and revised it

critically for important intellectual content, and gave final approval of the version to be published. SMC made substantial contributions to the conception and design of the study, to the analysis and interpretation of the data, and approved the version to be published.

Details of ethics approval

The Committee for Medical Research Ethics of Health Region IV, Norway, and The Norwegian Medicines Agency approved the study (no. 145-04; 23 September 2004). Written informed consent was obtained from each patient before inclusion, and the declaration of Helsinki was followed throughout the study. The study was conducted according to principles of 'Good Clinical Practice', and the trial is registered at ClinicalTrials.gov as NCT00159536.

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