Anti-Müllerian-inhibiting hormone receptor 2 (AMHR2) polymorphism and risk for Polycystic Ovary Syndrome (PCOS): Relationship to Gonadotropin Levels.

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Introduction

Polycystic Ovary Syndrome (PCOS)

- Clinical or biochemical hyperandrogenemia
- Chronic anovulation
- Polycystic ovarian morphology in U/S

} 2 out of 3

Rotterdam criteria, ESHRE/ASRM, 2003

Genetic predisposition

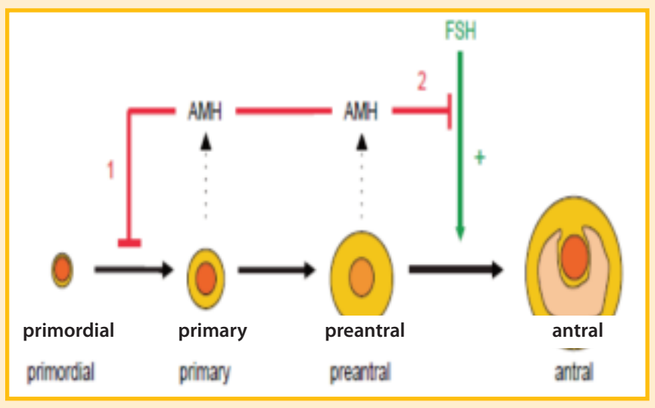
	MZF r (95% CI)	DZF/sisters r (95% CI)
Oligomenorrhea	0.67 (0.49 to 0.80)	0.07 (-0.19 to 0.34)
Acne	0.78 (0.69 to 0.84)	0.44 (0.30 to 0.56)
Hirsutism	0.86 (0.75 to 0.92)	0.28 (0.05 to 0.50)
PCOS	0.71 (0.43 to 0.88)	0.38 (0.00 to 0.66)

MZF, Monozygotic females; DZF/sisters, dizygotic females twins and nontwin sisters.

Vink et al, 2006

AMH: In the ovary

- AMH is expressed throughout the early stages of folliculogenesis up to the stage of antrial follicles with diameter up to 4mm.
- AMH is secreted by granulosa cells of follicles.
- AMH inhibits both the initiation of follicular development and the selection of the dominant follicle.

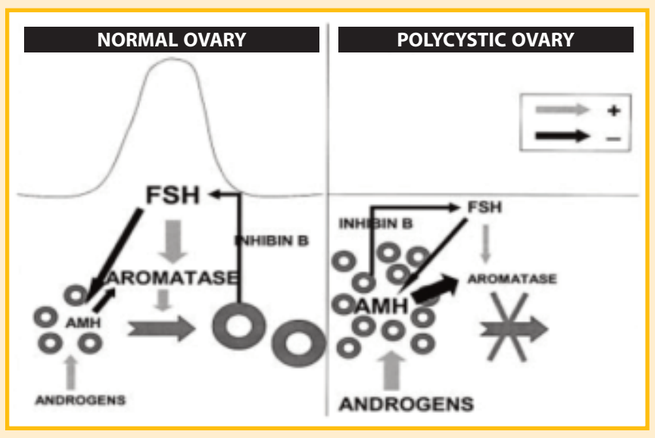


Model of AMH action in the ovary. Progressing stages of folliculogenesis are depicted. AMH is produced by the small growing (primary and preantral) follicles in the postnatal ovary and has two sites of action. It inhibits initial follicle recruitment (1) and inhibits FSH-dependent growth and selection of preantral and small antral follicles (2).

Visser et al, 2006

AMH in PCOS: Suspension of the selection of the dominant follicle

- PCOS: 2-6 fold increase in follicular number (pre-antral and small antral follicles)
- Anovulatory PCOS: Interruption of follicular development beyond diameter of 6-9 mm, just before the selection of the dominant follicle.



Interactions between intra-ovarian androgens, number of selectable follicles, anti-Müllerian hormone (AMH) production and FSH effect on aromatase and on the selection of the dominant follicle, within the normal ovary (left panel, displaying the FSH inter-cycle peak) and PCO (right panel). In PCOS, the balance between FSH and AMH would turn towards AMH, which leads to *in vivo* defect of aromatase activity and follicular arrest. The excess of AMH would be the consequence of the excess of antral follicles. In turn, this follicle excess would be the result of intra-ovarian hyperandrogenism. The negative feed-back exerted by inhibin B would not be the culprit. A proper balance between FSH and AMH can be restored by cautious increase of AMH in PCOS. Indeed, the inhibiting physiological effect of FSH on AMH is maintained with PCOS (from Pigny *et al*., 2003 and Jonard *et al*., 2003b).

Jonard et al, 2004

Aim of the study

Investigation of the role of AMH receptor II AMHR2 -482 A>G (rs2002555) in the pathogenesis of polycystic ovary syndrome (PCOS).

Subjects and methods

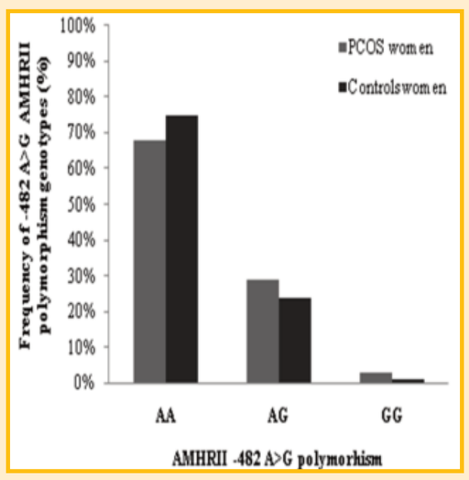
- 858 PCOS women of age 23.73±5.83 years and body mass index (BMI) 26.59±7.07kg/m^2 and 312 ovulatory co ntrolswere included in the study.
- No statistically significant difference in BMI between PCOS women and controls was observed in the study.
- PCOS: Rotterdam criteria
- Clinical hyperandrogenism: Hirsutism (Ferriman-Gallwey score≥ 8) or/and alopecia
- Anovulation: Serum progesterone<10 ng/mL in two consecutive cycles

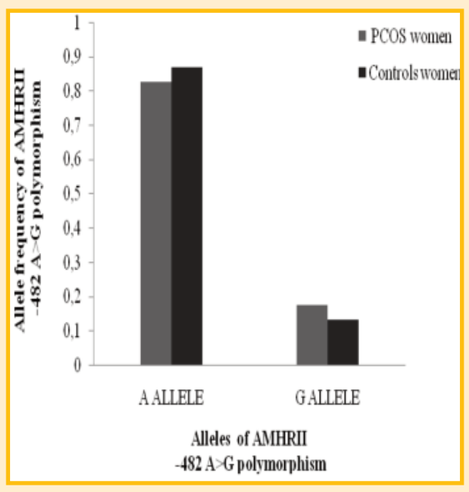
Results

Prevalence of AMHR2 -482 A>G polymorphism in PCOS women and controls

	AA	AG	GG	p value
PCOS	585 (68.2%)	248 (28.9%)	25 (2.9%)	0.026
Controls	234 (75%)	74 (23.7%)	4 (1.3%)	

Genotype of AMHR2 -482 A>G polymorphism and allele prevalence in PCOS women and controls





Clinical and hormonal characteristics of PCOS women considering the AMH receptor-482 A>G polymorphism genotype

	PCOS (n=702)	PCOS AA (n=488)	PCOS AG (n=195)	PCOS GG (n=19)	p value
AGE	24.02±5.82	24.25±5.73	23.53±5.86	23.34±7.32	0.172
BMI (kgr/m^2)	26.55±6.98	26.40±6.70	26.88±7.48	27.38±8.78	0.875
WAIST/ HIP	0.79±0.25	0.78±0.07	0.81±0.46	0.80±0.08	0.668
AMH	5.88±6.03	5.18±2.61	5.82±1.84	4.11±2.38	0.688
FSH (mIU/ml)	5.99±1.80	5.99±1.84	6.05±1.69	5.27±1.62	0.197
LH (mIU/ml)	7.69±5.35	7.78±5.18	7.77±5.88	4.43±2.43b,d	0.003
LH:FSH Ratio	1.34±0.93	1.36±0.91	1.34±0.98	0.83±0.41b,d	0.010
DHEAS μg/dl)	3013±1315	3044±1310	2986±1293	2475±1596	0.152
PRL (ng/ml)	14.20±7.17	14.64±7.32	13.48±6.81	10.07±4.54 b	0.004
TESTO (ng/dl)	74.69±29.58	75.36±30.19	74.11±28.53	63.33±22.37	0.146
Δ4 (ng/ml)	2.77±1.07	2.78±1.07	2.81±1.10	2.33±0.79	0.194
17OH (ng/ml)	1.13±0.56	1.12±0.55	1.16±0.60	1.06±0.49	0.856
SHBG (nmol/l))	43.39±26.82	44.15±27.94	42.07±24.48	37.34±18.77	0.477
FAI	8.37±6.83	8.35±6.86	8.58±7.04	8.37±6.83	0.812

Clinical and hormonal characteristics of controls considering the AMH receptor-482 A>G polymorphism genotype

	Controls (n=97)	Controls AA (n=75)	Controls AG (n=21)	Controls GG (n=1)	p value
AGE	30.85±5.76	30.93±5.94	30.57±5.32	31	0.970
BMI (kgr/m^2)	27.23±6.89	26.76±6.63	28.72±7.82	30.84	0.455
WAIST/ HIP	0.78±0.07	0.78±0.07	0.77±0.07	0.79	0.825
AMH	3.12±1.36	3.2±1.39	2.85±1.36	-	-
FSH (mIU/ml)	6.93±2.39	7.19±2.55	6.13±1.46	4.53	0.118
LH (mIU/ml)	5.61±2.71	5.88±2.82	4.52±2.04	7.96	0.085
LH:FSH Ratio	0.85±0.40	0.87±0.42	0.74±0.27	1.76	0.118
DHEAS μg/dl)	1967±802	1955±806	2042±813	1323	0.660
PRL (ng/ml)	13.49±6.19	13.40±6.42	13.43±5.32	21.50	0.434
TESTO (ng/dl)	39.99±11.13	39.78±11.24	41.05±11.09	33	0.741
Δ4 (ng/ml)	1.71±0.47	1.72±0.46	1.68±0.52	1.41	0.775
17OH (ng/ml)	0.79±0.39	0.81±0.38	0.71±0.42	0.52	0.448
SHBG (nmol/l))	60.44±32.86	59.65±30.91	62.79±40.42	70.81	0.748
FAI	2.91±1.65	2.90±1.63	2.99±1.77	1.62	0.523

Conclusions

1. AMHR2 -482 A>G (rs2002555) polymorphism is implicated in the pathogenesis of PCOS.
2. AMHR2 -482 A>G (rs2002555) polymorphism is related to decreased LH levels in women with PCOS.

AMHR2 -482 A>G (rs2002555) polymorphism and decreased LH levels in women with PCOS.

Controls- Ovulatory PCOS
LH: No impact on AMH levels
LH: Decreased AMHR2 expression

Oligo-/Anovulatory PCOS
LH: Increased AMH levels
LH: No down-regulation in AMHR2 expression

Pierre et al, 2013

In the present study

AMHR2 -482 A>G (rs2002555) polymorphism resulting in decreased AMH signaling is related to decreased LH levels, corroborating the positive relationship between AMH and LH, which has been confirmed in PCOS.