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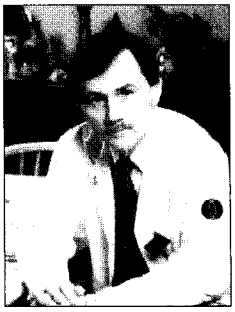

1997-1998	President, Society for Gynecologic Investigation
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The Role of Mullerian Inhibiting Substance (MIS) in Ovarian Physiology and the Clinical Utility of its Measurement

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Mullerian Inhibiting Substance (MIS) or anti mullerian hormone (AMH) is a 72-D dimeric glycoproprotein which is a member of the TBFβ family. It is best known in male reproductive physiology as the product of sertoli cells which causes the regression of the mullerian ducts in the fetus[1]. In its absence, mullerian ducts (uterus and tubes) may be found in otherwise normal genetic males. However, emerging evidence suggests a very important role for MIS in female ovarian physiology and as an important clinical marker.

MIS is secreted in the ovary by the granulosa cells of prenatal follicles (6 mm)[2]. Secretion begins in the female fetus at 36 weeks of gestation and is higher postnatally and in childhood and then gradually decreases throughout reproductive life[3]. Levels are largely undetectable at the time of menopause[4].

MIS appears to be secreted by preantral follicles in the transitional state from primordial follicles to dominant antral follicles. At this time these larger follicles cease to produce MIS[5]. There is evidence to suggest that MIS has several physiological effects in the ovary. These largely paracrine effects will be described below.

MIS acts through specific receptors signaling through a serine threonine kinase receptor complex. Downstream signaling is similar to that which occurs in other member of the TGFβ family involving Smad proteins[6].

The section of MIS by smaller preantral follicles appears to suppress the development of the growing dominant follicle and in the absence of MIS, as demonstrated in a transgenic MIS-knockout mouse model; multiple larger follicles are found which ultimately leads of early depletion[7].

The direct mechanism whereby MIS may inhibit follicular development has been demonstrated in various animal models. These include the following mechanisms inhibition of aromatase activity[8], decreasing the number of LH receptors[9] and the regulation of testosterone production by theca cells [10]. There are also data suggesting that MIS influences the sensitivity of follicles to FSH[11]. On an individual follicle basis it has been found that the pattern of expression of MIS within follicles may be different, with lower expression in some follicles rendering them more sensitive to FSH, allowing for growth and the emergence of follicular dominance[12].

Clinical applications of measuring serum MIS

MIS has proved to be a useful measurement in a variety of clinical circumstances. To date the

most useful application of early follicular phase measurements (day 2-3) is for the prediction/ assessment of ovarian reserve[13,14]. However, serum MIS may also be useful for predicting the response to gonadotropin and hyperstimulation risk in normal women[15]. MIS also undergoes interesting excursions during gonadotropin stimulation resulting in follicular growth, which reflects the physiology behind the role of MIS[16]. Finally serum MIS maybe useful as a diagnostic aid in PCOS, reflecting its enhanced secretion associated with abnormal ovarian morphology[16,17].

MIS as a marker of ovarian reserve

Several studies have shown that levels of MIS reflect ovarian reserve, with low levels suggesting a diminished ovarian reservoir and a poor response to gonadotropin stimulation. Studies comparing MIS to E2, FSH and inhibin B have shown that MIS reflects ovarian reserve better than other hormonal markers[13,18,19]. Fig. 1 depicts the ROC curve for MIS compared to the other markers. Using a cut off value of approximately 0.25 ng/ml affords a sensitivity and specificity of approximately 90%. Our own data also supports this observation. Accordingly we are actively using day 2 MIS levels clinically to counsel patients regarding their prognosis of responding to gonadotropins, yet not necessarily their potential for a successful pregnancy. An advantage of serum MIS is that there is less cycle to cycle variation in this measure compared to FSH.

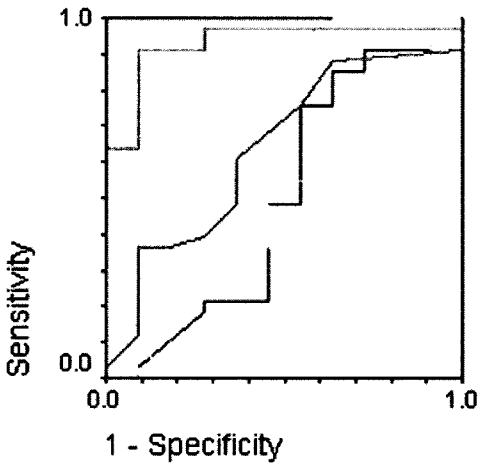

Fig. 1.

Cycle excursions and the risk of hyperstimulation

MIS reflects preantral follicular secretion and the suppression of dominant follicular activity early in the cycle. In normal cycles or those stimulated with gonadotropins, as antral follicles emerge, MIS levels decline[16]. We have observed a related phenomenon, in the opposite direction, whereby GnRH agonist suppression, as used in the long protocol for IVF-ET cycles, results in higher levels of MIS[20]. This presumably reflects the suppression of follicular activity by inhibition of LH/FSH allowing the secretion of MIS from the smaller preantral follicles.

Since day 2 MIS reflects the pool of available preantral follicles which may be recruited for follicular development, we have found that in normal women, day 2 MIS significantly reflects the risk of hyperstimulation when gonadotropins are used[15] (Table 1). Surprisingly, this is not the case in women with PCOS who have elevated levels (see below), presumably because of some difficulty in the transition or selection of follicles going from preantral to antral follicles in PCOS[20].

Table 1.

Characteristics of patients with normal ovarian response (group A) compared to those with ovarian hyperstimulation syndrome (group B).

	A (n = 14)	B (n = 16)	*P* value
Age (y)	29.9 ± 0.8 (25–35)	29.9 ± 0.7 (24–34)	.95
Weight (lb)	149.2 ± 11.0 (110–175)	140.2 ± 8.3 (108–230)	.54
Day 2 E_2 (pg/mL)	38.3 ± 4.3 (21–62)	43.7 ± 3.1 (19–60)	.65
Day 2 FSH (IU/mL)	5.4 ± 0.4 (2.8–8.1)	4.6 ± 1.5 (1.8–7.3)	.32
Days of stimulation	10.8 ± 0.2 (10–14)	10.1 ± 0.2 (9–11)	.02
Cum. gonadotropin dose (IU)	2,508.4 ± 156.8 (1,275–3,375)	2,254.7 ± 129.6 (1,275–3,300)	.19
# of follicles >18 mm	9.7 ± 0.9 (5–14)	24.25 ± 2.2 (15–39)	<.001
Follicular sensitivity (IU/follicle)	288.8 ± 33.3 (116.7–450)	103.7 ± 10.9 (53.1–214.3)	.0032
Peak E_2 (pg/mL)	1,627.2 ± 88.7 (945–1,971)	4,492.4 ± 232.3 (3,598–6,511)	<.001
Day 2 MIS (ng/mL)	0.63 ± 0.09 (0.21–1.17)	3.62 ± 0.87 (0.24–13.17)	.0036

Note: Data are presented as mean ± SEM (range).

Nakhuda. Serum MIS predicts risk of OHSS. Fertil Steril 2006.

Finally there is some evidence that MIS levels at the time of HCG administration may reflect the health of the oocytes aspirated and embryos generated with IVF-ET[21]. Serum levels also seem to reflect intrafollicular levels[22]. Much more work needed to completely to fully understand the local control MIS may have in follicle dynamics.

MIS reflecting PCOS morphology

MIS levels are elevated in PCOS[16,17] (Fig. 2) and reflects the altered ovarian morphology. MIS also correlates with androgen levels in PCOS. This is most likely because of the presence of multiple smaller preantral follicles in PCOS. However, in our hands, we were not able to use a cut off level of MIS to detect or predict PCOS[17]. This, possibly, may be because of the heterogeneity of the disorder. Recent data suggest that metformin treatment in women with PCOS may decrease levels of serum MIS, presumably in association with improvement in follicular activity[23,24].

In that serum MIS appears to reflect abnormal cystic ovarian morphology, it is attractive to hypothesize that MIS may be useful in the diagnosis of early PCOS when ultrasound and clinical data may be difficult to establish, for example in young girls. This hypothesis remains to be tested and proved.

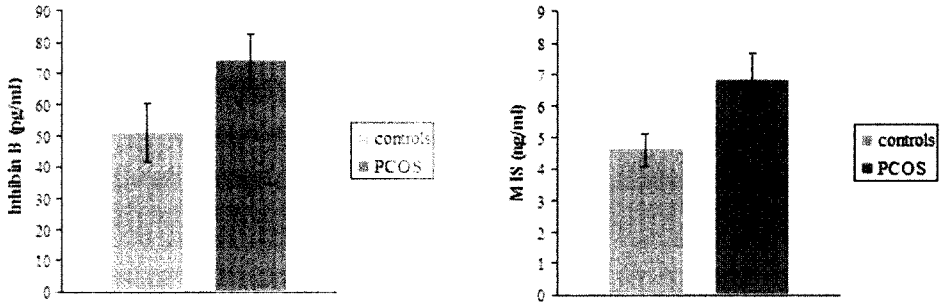

Fig. 2.

Conclusion

MIS in women appears to be an important factor in ovarian physiology. In that it plays a pivotal role in follicular dynamics renders it an extremely valuable marker in a variety of clinical situations, most important of which is as a reflection of decreased ovarian reserve.

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