A case report supporting the concept that a role for the anti-Müllerian hormone (AMH) in normal folliculogenesis is to diminish the biological activity of follicle stimulating hormone (FSH)

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Summary

Purpose: To describe a case where a woman was ovulating with regular menses despite very low sera follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Case Report: Serum anti-Müllerian (AMH) was obtained because the woman was to be an egg donor for her identical twin sister. This 28-year-old woman responded fairly well to controlled ovarian hyperstimulation producing ten metaphase II eggs and eight fertilized and were cryopreserved on day 3. Her serum AMH level was subnormal at 0.6 ng/mL. Conclusions: This case suggests that FSH may be more biologically active in the presence of low AMH.

Key words: Decreased oocyte reserve; Anti-Müllerian hormone; Gonadotropin deficiency; FSH induced aromatase enzyme.

Introduction

During folliculogenesis, the one antral follicle amongst the cohort of antral follicles present in the early follicular phase is the one that can be converted from an androgen dominant follicle to an estrogen dominant follicle despite the dropping serum levels of follicle stimulating hormone (FSH). This is related to negative feedback to the pituitary from the rising serum estradiol (E2) levels for FSH release from the pituitary [1]. The anti-Müllerian hormone (AMH) plays a role in the selection of the dominant follicle [1]. It is detected in the granulosa cells of early primordial follicles. However, the peak levels are found in small antral follicles [2]. One of the ways that FSH helps to select a dominant follicle is by helping in the conversion of androgen to estrogen by helping to simulate the FSH induced aromatase enzyme [1]. AMH inhibits FSH induced aromatization. This may be a mechanism present to allow only one dominant follicle to form each cycle. Possibly the one antral follicle with the lowest AMH concentration in the granulosa cell is the one that becomes the dominant follicle. By this theory, the follicles with higher AMH content will not be able to aromatize the androgen by FSH to estradiol (E2) related to relative FSH resistance because of higher AMH levels, and thus they undergo atresia [1]. This could explain why women with polycystic ovarian syndrome, who have high levels of serum AMH, possibly related to a higher level of production of AMH by these early follicles, despite adequate serum FSH, fail to ovulate related to FSH resistance. However, these women will respond to increased levels of serum FSH induced by competitive inhibition of estrogen negative feedback on the pituitary (as seen with selective estrogen receptor modulators, e.g., clomiphene citrate), or lowering serum E2 (and thus negative feedback on the pituitary) with aromatase inhibitors, e.g., letrozole, or simply raising FSH by injecting gonadotropins [3]. At mid-cycle the FSH secreted by the pituitary has a greater biological activity [4, 5]. The possibility exists, though not proven, is that one mechanism of AMH decreasing follicular sensitivity to FSH is by inhibiting the mid-cycle production of the molecular form of FSH with greater biologic activity.

Reported herein, is a case that will support the concept that one of the roles of AMH may be to decrease the biological activity of FSH at mid-cycle.

Case Report

A 28-year-old woman was asked to be an oocyte donor for her identical twin sister who was in premature ovarian failure with a serum AMH of 0.03 ng/mL. The sister’s serum FSH was 87 mIU/mL. Her ovarian failure was attributed to endometriosis and two laparoscopic surgeries. The egg donor sister had regular menstrual cycles, but interestingly, her day 3 serum FSH and LH were both less than 1.0 mIU/mL. Yet her serum AMH was low at 0.6 ng/mL. For her oocyte retrieval cycle, there were only four antral...
folicles serum on day 1 of the cycle. She was given 150 IU FSH and 150 IU human menopausal gonadotropins (hMG). On day 13 she had in the left ovary follicles with average diameter measuring (mm) 19.6, 21, 21.3, 16, and 10.3 and in the right ovary 19, 21, 21, 13.6, 13.3, 11.6, and 12.

The peak serum E2 was 1,909 pg/mL, the serum progesterone was 0.57 ng/mL, the serum LH was 1 mIU/mL, and the FSH was 20.4 mIU/mL (related to exogenous FSH administration). The total number of metaphase II oocytes retrieved was ten, and eight fertilized. They were cryopreserved on day 3 for future transfer to her identical twin sister.

Discussion

The best explanation for a low FSH, along with a low AMH, and a low antral follicle count is that there was, indeed, diminished oocyte reserve, but there must have been another problem with the woman’s developing diminished gonadotropins. This could be early hypopituitarism affecting only the gonadotropins, which are more sensitive to noxious influences since the other pituitary stimulated hormones (thyroid and cortisol) were normal. The big question is how could she have regular menses with evidence of ovulation in natural cycles with such low gonadotropins? One hypothetical explanation is that the FSH that she was making was more biologically active related to low AMH. This case may suggest that one of the functions of AMH in normal folliculogenesis is to reduce the biological action of FSH. It could also suggest that the one follicle in the cohort of antral follicles may be able to become estrogen dominant, and thus control its own destiny to become the dominant follicle; this is because that follicle has the least amount of AMH in the granulosa cells, and thus is able to produce adequate FSH induced aromatase enzyme, despite dropping serum FSH related to negative feedback of estrogen on the FSH secreting cells of the pituitary. Based on this case, however, there is a suggestion that the mechanism of AMH inhibiting FSH-induced aromatase enzyme may be also by reducing the biological activity of FSH.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest

The authors declare no conflict of interest.

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References

[1] Check J.H.: “Understanding the physiology of folliculogenesis serves as the foundation for perfecting diagnosis and treatment of ovulatory defects”. Clin. Exp. Obstet. Gynecol., 2012, 39, 273.
[2] Durlinger A.L., Grijters M.J., Kramer P., Karels B., Ingraham H.A., Nachtigal M.W., et al.: “Anti-müllerian hormone inhibits initiation of primordial follicle growth in the mouse ovary”. Endocrinology, 2002, 143, 1076.
[3] Check J.H.: “The future trends of induction of ovulation”. Minerva Endocrinol., 2010, 35, 227.
[4] Marut E.L., Williams R.F., Cowan B.D., Lynch A., Lerner S.P., Hodgen G.D.: “Pulsatile pituitary gonadotropin secretion during maturation of the dominant follicle in monkeys: estrogen positive feedback enhances the biological activity of LH”. Endocrinology, 1981, 109, 2270.
[5] Anobile C.J., Talbot J.A., McCann S.J., Padmanabhan V., Robertson W.R.: “Glycoform composition of serum gonadotrophins through the normal menstrual cycle and in the post-menopausal state”. Mol. Hum. Reprod., 1998, 4, 631.

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