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Normogonadotropic azoospermia: the puzzle of hormonal treatment

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Abstract

The editorial proposes an original algorithm for hormonal treatment of patients with normogonadotropic azoospermia (NOAN). This condition is very common in clinical practice, and the approach of endocrinologists varies. Different therapeutic strategies are recommended based on clinical (testicular volume and body mass index) and hormonal parameters (inhibin B and 17-alpha hydroxyprogesterone levels). The algorithm suggests the role of follicle-stimulating hormone or chorionic gonadotropin, or incretin therapy, which are fully included in the potential therapeutic proposal due to the significant repercussions of metabolic syndrome and obesity on sperm quality.

Editorial

Azoospermia conditions are traditionally classified into obstructive (OA) and non-obstructive (NOA) forms. In OA, testicular function is preserved. In NOA, testicular spermatogenesis is impaired. In NOA, elevated FSH levels and decreased inhibin B levels are the two most specific markers of impaired testicular function. However, there is a large number of NOA patients with normal FSH levels, defined as normogonadotropic azoospermia (NOAN) (1,2).

In clinical practice, among NOAN patients, it is possible to identify those with reduced testicular volume (12 ml) and normal testicular volume (3), while on the endocrine level, those with normal and reduced Inhibin B levels (4). NOAN patients can be further classified based on metabolic phenotype into metabolically healthy and obese NOAN (5).

From a seminological and histopathological point of view, the main difference characterizing NOAN vs NOA concerns a greater damage to the post-meiotic phase of spermatogenesis, confirmed by the increase in the number of spermatids (round and elongated) in the semen analysis (2). From an endocrine point of view, the post-meiotic phase of spermatogenesis is FSH independent and modulated by intratesticular testosterone levels. NOAN patients characteristically have normal serum concentrations of total testosterone. It is not easy to estimate the ratio between serum testosterone and intratesticular testosterone, theoretically 1 to 100. From this point of view we have recently highlighted how a threshold value of 17AlphaHydroxyProgesterone (17OHPg) equal to 1.18 ng/ml identifies a cut-off associated with a lower response to pharmacological treatment with follicle stimulating hormone in a selected population of infertile men, suggesting that this marker can be considered a parameter capable of suggesting a possible alteration of testicular steroidogenesis characterized by accumulation of upstream precursor and reduction of intratesticular testosterone levels, since 17OHPg, through the action of 17-20 lyase, is transformed into androstenedione, a precursor of testosterone synthesis (6).

Based on this consideration, NOAN patients could be further classified into NOAN with 17-alpha-hydroxyprogesterone levels lower or higher than the threshold value of 1.18 ng/ml. This leads to the possibility of finding different combinations of NOAN phenotypes in clinical practice, as reported in **Table 1**.

Table 1. Subclassification of patients with NOAN.

For testicular volume
- NOAN with normal testicular volume
- NOAN with reduced testicular volume (< 12 ml)
For inhibin B levels
- NOAN with normal inhibin B levels
- NOAN with reduced inhibin B levels
For body weight and waist circumference
- Metabolically healthy NOAN
- Metabolically obese NOAN (BMI > 30; waist circumference > 102 cm)
For 17-alpha-hydroxyprogesterone levels
- NOAN with 17-alpha-hydroxyprogesterone levels < 1.18 ng/ml
- NOAN with 17-alpha-hydroxyprogesterone levels > 1.18 ng/ml

Of the 8 possible clinical combinations, it follows that two conditions in particular may occur, with a favorable or unfavorable expected spermatogenetic prognosis, as reported in **Table 2**.

Table 2. NOAN with favorable and unfavorable expected spermatogenetic prognosis.

NOAN with favorable expected spermatogenetic prognosis - normal testicular volume + normal inhibin B levels + metabolically healthy + 17-alpha-hydroxyprogesterone levels < 1.18 ng/ml
NOAN with unfavorable expected spermatogenetic prognosis - reduced testicular volume + reduced inhibin B levels + metabolically obese + 17-alpha-hydroxyprogesterone levels > 1.18 ng/ml

On the pharmacological level, according to the possible phenotypic combinations that include a category of patients with mild or moderate alteration of the Sertolian function (reduced testicular volume and/or reduced levels of Inhibin B) (2-4), on the basis of the endocrine regulation characteristics of the post-meiotic phase of spermatogenesis (2) and in accordance with the potential effects that visceral obesity can exert on the pituitary-testicular axis (5), three pharmacological options for the treatment of NOAN patients could be proposed **(Table 3 and Table 4).**

Table 3. Pharmacological treatment in patients with NOAN according to the possible clinical phenotype.

Phenotype	**Therapy**
For testicular volume	
- NOAN with normal testicular volume	HCG only
- NOAN with reduced testicular volume (< 12 ml)	FSH and HCG
For inhibin B levels	
- NOAN with normal inhibin B levels	HCG only
- NOAN with reduced inhibin B levels	FSH and HCG
For BMI and waist circumference	
- Metabolically healthy NOAN	HCG only
- Metabolically obese NOAN (BMI > 30; waist circumference > 102 cm)	HCG + GLP1 receptor agonist or GIP-GLP1 receptor dual agonist
For 17-alpha-hydroxyprogesterone levels	
- NOAN with 17-alpha-hydroxyprogesterone levels < 1.18 ng/ml	HCG only HCG
- NOAN with 17-alpha-hydroxyprogesterone levels > 1.18 ng/ml	HCG alone (high dose)

Legend: HCG (human chorionic gonadotropin); FSH (follicle stimulating hormone)

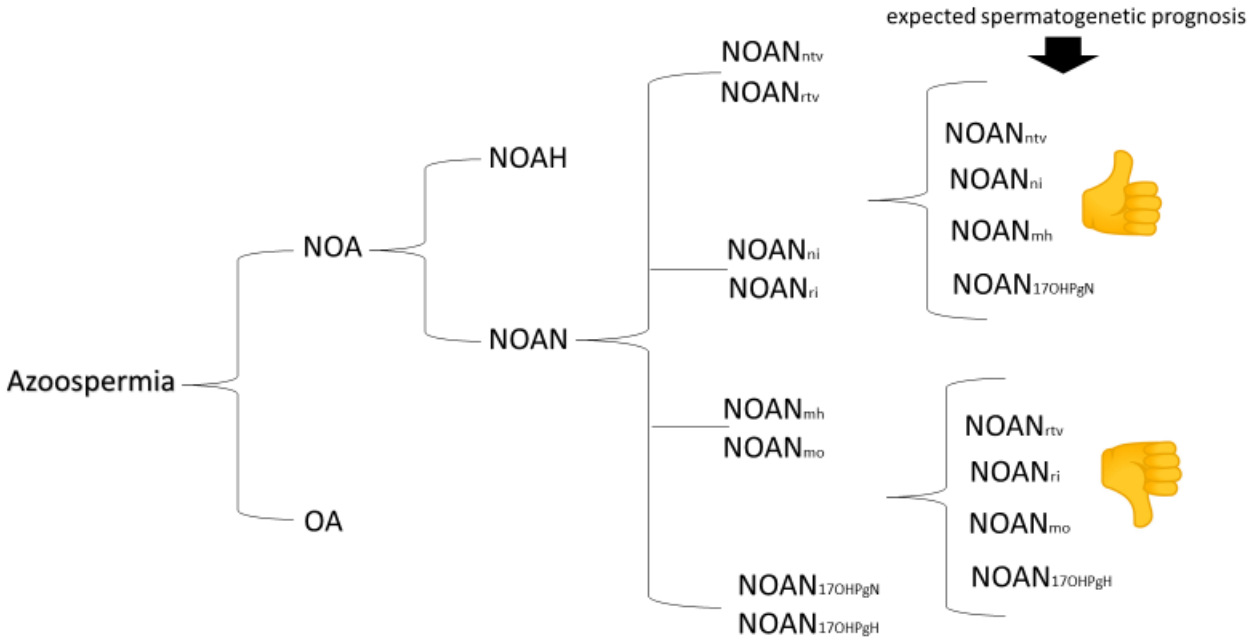
Table 4. Pharmacological therapy in patients with NOAN according to the different expected spermatogenetic prognosis.

Expected spermatogenetic prognosis	**Therapy**
NOAN with favorable expected spermatogenetic prognosis - normal testicular volume + normal inhibin B levels + metabolically healthy + 17-alpha-hydroxyprogesterone levels < 1.18 ng/ml	HCG alone
NOAN with unfavorable expected spermatogenetic prognosis	FSH + HCG + GLP1 receptor agonist or GIP-GLP1 receptor dual agonist

- reduced testicular volume + reduced inhibin B levels + metabolically obese + 17-alpha-hydroxyprogesterone levels > 1.18 ng/ml	

Legend: HCG (human chorionic gonadotropin); FSH (follicle stimulating hormone)

Figure 1 summarizes an original classification scheme applicable in clinical practice for patients with azoospermia.



Acronym legend: OA (obstructive azoospermia); **NOA** (non-obstructive azoospermia); **NOAH** (hypergonadotropic non-obstructive azoospermia); **NOAN** (normogonadotropic non-obstructive azoospermia); **ntv** (normal testicular volume); **rtv** (reduced testicular volume; **ni** (normal inhibin levels); **ri** (reduced inhinbin levels); **mh** (metabolically healthy); **mo** (metabolically obese); **17OHPgN** (levels of 17OHPg < 1.18 ng/ml); **17OHPgH** (levels of 17OHPg > 1.18 ng/ml).

Declarations

Conflict of Interest

The Authors declare that there is no conflict of interest.

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