

## Research Article

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Francesco Molinaro, Elisa Cerchia, Alfredo Garzi\*, Francesco Maria Severi, Rossella Angotti, Felice Petraglia, Mario Messina

# Serum levels of Inhibin B in adolescents after varicocelelectomy: A long term follow up

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**Abstract:** Introduction: To study the impact on adult's fertility of serum inhibin B levels in adolescent patients with idiopathic varicocele after minimally invasive surgical correction and to compare fluctuation of pituitary-testis hormonal values and testicular volumes. Materials and Methods: A case-control study was carried out on a group adolescent patients (n=60) affected by idiopathic left varicocele (group V) and compared with control adolescents (n=40) in the Paediatric Surgery Section of Siena (from June 1993 till September 2013). Inhibin B levels and testicular volume before (T0) and after at 6 and 12 months from surgery (T1 and T2) were evaluated. Results: A positive correlation between testicular growth at T1 and T2 ( $P<0.001$ ) was found. Linear regression analysis showed a positive correlation between inhibin B levels and testicular volume (expressed as the sum of the right and left values) ( $P<0.0001$ ). Conclusions: Inhibin B levels are a valid marker for studying the effects of varicocele on the testicular function and confirm the necessity of early surgical correction for preventing the trophic testicular damage and male infertility.

**Keywords:** Lung Sparing Surgery, intralobar pulmonary sequestration, pediatric thoracic surgery

\*Corresponding author: Alfredo Garzi, Department of Medicine and Surgery, Pediatric Surgery, Piazza Sergardi, 16, 52044 Cortona (AR) Italy, E-mail: agarzi@unisa.it

Francesco Molinaro, Elisa Cerchia, Rossella Angotti, Mario Messina, Division of Pediatric Surgery, Department of Medical, Surgical and Neurological Sciences, University of Siena, Italy

Francesco Maria Severi, Felice Petraglia, Obstetrics and Gynecology, Department of Molecular and Developmental Medicine, University of Siena, Italy

## 1 Introduction

Varicocele is the most commonly diagnosed pre-pubertal andrological condition, with an impact on adult's fertility. It has an incidence of 10-15% between adolescents [1].

A time-dependent decline in testicular function has been clearly documented in children with varicocele [2]. An open debate exists on the gold standard of surgical treatment and follow up (timing and existence of predictive factors of outcome).

Inhibin B is a glycoprotein secreted by Sertoli cells that has a role in the control of spermatogenesis, through a mechanism of negative feedback on follicle stimulating hormone (FSH) secretion. This mechanism is activated during pubertal stage G3 according to Tanner's classification [3]. Serum inhibin B levels are low and correlated with testicular volume in patients with varicocele during Tanner stages G4/G5 [4]. Surgical treatment in adult's varicocele increases serum inhibin B levels in the postoperative period, with positive effects on testicular viability [5].

The aim of the present study was to analyze inhibin B in adolescent patients with idiopathic varicocele after minimally invasive surgical correction, comparing fluctuation of hormonal values and testicular volumes.

## 2 Materials and methods

A case-control study was carried out on a population of adolescent patients (n=60) with idiopathic left varicocele of grade III after Horner (group V), in the Paediatric Surgery Section of Siena (from June 1993 to September 2013). The pathology was diagnosed after clinical examination and confirmed by colour Doppler sonography of the spermatic vessels. All patients in the study population were in pubertal stages classifiable as between G4 and G5 according to Tanner's classification. These patients were compared to control adolescents (n=44) – who were not affected by endocrine pathologies – with the same Tanner

stages G4-G5 (group C). Informed consent was requested and obtained from both groups, following authorization by the local Ethics Committee. The patients in group V had a mean age at diagnosis of 15.5 years (range: 12.5-17 years); group C had a mean age of 15.1 years (range: 13-16.5 years).

At diagnosis (T0) blood samples were taken from all patients to assess basal serum inhibin B levels and testicular volume was determined by clinical evaluation and ultrasound exam. Palomo varicocelelectomy through a minimally invasive approach was performed in all cases within one month of diagnosis.

After surgery, all patients were submitted to a follow up evaluation (6 and 12 months) by measuring serum inhibin B levels and testicular volume (T1 and T2, respectively). All data are expressed as mean and median  $\pm$  2 standard error of mean (SEM). The differences in serum inhibin B levels between the two groups were compared by an unpaired t-test with Welch's correction, while testicular volumes were compared by a paired t-test. Qualitative analysis between independent variables was done by linear regression analysis. The differences were considered significant in all cases in which the P value was below 0.05.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

### 3 Results

Serum inhibin B levels and testicular volume at T0, T1 and T2 are reported in Table 1. Inhibin B values in patients at T0 were lower than in controls ( $P < 0.0001$ ); inhibin B values between T1 and T2 showed a significant increase (Figure 1). Left testicular volume of patients was lower than in controls at T0 ( $P < 0.0001$ ), but not at T2 ( $P = 0.7841$ ). A positive correlation was found between testicular growth at T1 and T2 ( $P < 0.001$ ) (Figure 2).

Linear regression analysis showed a positive correlation between inhibin B values in group V and testicular volume (expressed as the sum of the right and left values) ( $P < 0.0001$ ) (Figures 3).

### 4 Discussion

The correlation between varicocele and infertility is of particular interest since varicocele has a negative effect on spermatogenesis [6]. The restoration of fertility in an

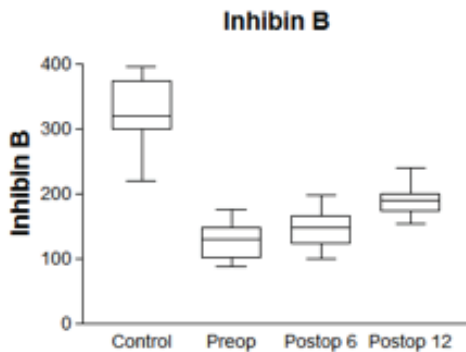


Figure 1: Statistical analysis about serum levels of inhibin B.

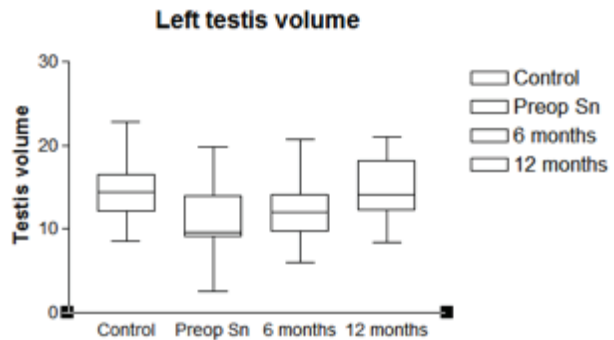


Figure 2: Statistical analysis about left testis volumes expressed in ml.

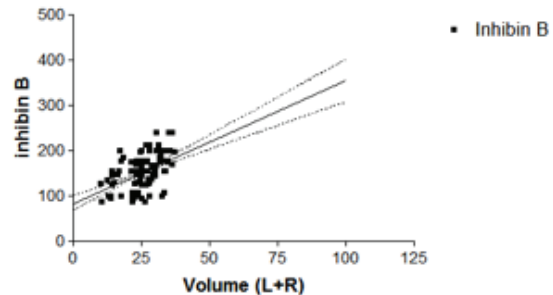


Figure 3: Linear regression analysis between inhibin B values and testicular volumes expressed as L+R.

**Table 1:** Values expressed as mean  $\pm$  standard error of mean serum levels of inhibin B and testicular volumes at T0, T1 and T2.

	PATIENTS			CONTROLS
	T0	T1	T2	
<b>INHIBIN B (pg/ml)</b>	125.3 $\pm$ 3.603	145.1 $\pm$ 3.819	190.8 $\pm$ 3.027	324.6 $\pm$ 6.512
<b>RIGHT VOLUME (ml)</b>	12.44 $\pm$ 0.521	12.84 $\pm$ 0.518	13.18 $\pm$ 0.528	14.68 $\pm$ 0.726
<b>LEFT VOLUME (ml)</b>	10.83 $\pm$ 0.535	12.02 $\pm$ 0.461	14.75 $\pm$ 0.463	14.55 $\pm$ 0.561

azoospermic patient following correction of the venous pathology of the pampiniform plexus has been clearly shown [7]. However, the mechanisms by which varicocele negatively affects spermatogenesis are still unknown, but effects on hormonal dysfunctions on the hypothalamus-hypophysis/pituitary-gonad axis may be suggested [8].

The effect of varicocelectomy on fertility and improvements in sperm concentration, motility and testicular volume has been reported [8,9], even though recent randomized trials have highlighted contradicting results concerning the effects of varicocelectomy on fertility [9,10].

Serum inhibin B levels are recognized as high sensitivity and specificity markers of spermatogenesis [11]. This glycoprotein is produced/secreted by Sertoli cells and directly by spermatid cells in response to FSH and regulates the production of FSH via negative feedback to the hypothalamus-hypophysis/pituitary axis. Inhibin B serum levels are positively correlated with sperm count, testicular volume and the state of the spermatogenic epithelium evaluated by biopsies on testicular tissue [11,12]. Starting from the hypothesis that serum levels of inhibin B reflect the functionality of Sertoli cells in the presence of germinal cells, inhibin B levels were evaluated in adolescent varicocele [11]. Studies carried out on adult patients with varicocele showed a positive correlation between serum levels of inhibin B and sperm concentration following surgical correction. Pierik *et al.* demonstrated an increase in inhibin B concentration following surgical treatment of varicocele, thus suggesting that corrective treatment may promote functional repair of Sertoli cells, with undoubtedly positive effects on fertility [11,13]. The same Authors pointed out that an increase in serum levels of inhibin B was associated with an increase in the number of sperm/sperm concentration and an improvement in motility [12].

While Romeo *et al.* demonstrated a difference between untreated adolescent patients with varicocele and healthy

controls in terms of basal serum concentrations of inhibin B [4], our study investigated both preoperative and postoperative aspects, and highlighted the reduced plasma concentrations of inhibin B in the preoperative period in varicocele patients in comparison to healthy controls (T0). Comparison between the inhibin B levels at 6 and 12 months (T1, T2) showed a statistically significant increase representing a sign of trophic improvement in post-varicocelectomy gonadic tissue and restoration of Sertoli cell function and spermatogenesis. At Tanner stages IV and V, in fact, the production of inhibin B is strongly influenced by the interaction between Sertoli cells and spermatids, which are very sensitive to variations in testicular temperature. The correction of varicocele ensures a reduction in scrotal temperature sufficient to bring about the functional restoration of spermatogenesis [13,14]. However, there is still a significant difference in inhibin B levels between surgically treated individuals and controls, meaning that long-term follow-up studies are necessary in order to identify any further increases in the serum inhibin B at a greater time from surgery.

The analysis of testicular volume highlighted a reduction in the left testicle in subjects with varicocele in comparison to controls at T0, demonstrating the effect of the pathology on testicular trophism in untreated subjects [15,16,17]. The right testicular volumes of subjects with varicocele were no different from controls. Trigo *et al.* reported an equally significant reduction in left testicular volume in patients with varicocele during Tanner stages III, IV and V. This can be explained by the hypothesis that varicocele may progressively damage seminiferous tubule function in the late phases of pubertal development [18]. The regression analysis conducted on the variations in testicular volume at T0, T1 and T2 and the increase in serum levels of inhibin B demonstrated a positive relationship between the two parameters, confirming that an increase in testicular volume is accompanied by a constant increase in inhibin B values.

## 5 Conclusion

In conclusion, our present study showed that inhibin B levels are lower in adolescent with idiopathic varicocele than in healthy controls and that surgical correction of varicocele brings an increase in inhibin B concentration in the postoperative period, supporting the importance of early treatment of the pathology to ensure the rapid functional restoration of spermatogenesis. Serum Inhibin B levels are a valid markers for studying the effects of varicocele, before and after varicocelectomy, on the testicular function confirming the necessity of an early surgical correction for preventing trophic testicular damage and male infertility.

**Conflict of interest statement:** Authors state no conflict of interest

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