Response of serum inhibin B and pro-αC levels to gonadotrophic stimulation in normal men before and after steroidal contraceptive treatment

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BACKGROUND: Testicular regulation of inhibin B may be influenced by the germ cell complement. METHODS: We examined the effects of gonadotrophin stimulation on serum inhibin B and pro-αC in 25 normal men at (i) control (stimulation test 1), (ii) after spermatogenic suppression induced by testosterone plus progestin treatment (stimulation test 2), and (iii) during spermatogenic recovery induced by FSH and/or hCG treatment (stimulation test 3). For each test, subjects received a single injection of 1200 IU FSH or 5000 IU hCG or both. RESULTS: Inhibin B and pro-αC fell with spermatogenic suppression (75 and 51% of pre-treatment baseline respectively, P < 0.05). Inhibin B response to FSH (130±144%) was similar in controls and after germ cell suppression. Pro-αC response after germ cell suppression compared with control was significantly increased (P < 0.05) with both FSH (210±229% versus 140±185%) and hCG (254±261% versus 145%). All treatments partially restored spermatogenesis with no clear relationship apparent between inhibin B and sperm count. CONCLUSIONS: We conclude that: (i) serum inhibin B and pro-αC are only partially gonadotrophin dependent, (ii) spermatogenic suppression does not modify inhibin B response to FSH but enhances pro-αC response to both FSH and hCG, and (iii) inhibin B is a poor marker of spermatogenesis in this model of gonadotrophic manipulation in normal men.

Key words: FSH/inhibin/LH/Sertoli cell/testosterone

Introduction

Inhibin exists as two biologically active forms, inhibin A and B, which share a common α-subunit linked to either a βA- or βB-subunit by a disulphide bond (Vale et al., 1988). Inhibin B is the primary form found in the adult male (Anawalt et al., 1996). It is now recognized that there is a reciprocal relationship between serum FSH and inhibin B (Anawalt et al., 1996; Illingworth et al., 1996; Anderson, 2001; Hayes et al., 2001; Meachem et al., 2001). In addition to the dimeric inhibin forms, the partially processed form of the free α-subunit (pro-αC) is found in the circulation. The testis is the primary circulatory source of both inhibin B and pro-αC as orchidectomy results in very low or non-detectable levels (Anawalt et al., 1996).

In-situ hybridization and immunocytochemical studies have revealed different patterns of α- and βB-subunit expression in the tissue depending on the developmental age and species studied (Bergh and Cajander, 1990; Forti et al., 1992; Vannelli et al., 1992; Majdic et al., 1997; Andersson et al., 1998). Using immunocytochemical methods, the α-subunit is localized to human spermatocytes, Sertoli and Leydig cells, while the βB-subunit is localized to Sertoli and Leydig cells and more controversially to spermatocytes and early spermatids (Bergh and Cajander, 1990; Forti et al., 1992; Vannelli et al., 1992; Majdic et al., 1997; Andersson et al., 1998).

The secretion of inhibin is controlled by many factors including gonadotrophins and intrinsic factors involving Sertoli, Leydig and germ cells. In normal men, a single large dose (3000 IU) of recombinant human FSH (rhFSH) led to a doubling of serum inhibin B levels, reaching a peak within 72 h (Anawalt et al., 1996) with more recent studies showing that a dose of 225 IU was ineffective (Kinniburgh and Anderson, 2001). A dose–response study showed that administration of rhFSH (1000, 2000 and 3000 IU) led to significant increases in inhibin B, with the later two doses showing a significantly greater area under the curve than placebo or 1000 IU rhFSH (Kamischke et al., 2001). Both FSH and hCG have been shown to significantly increase pro-αC levels (Kamischke et al., 2001; Kinniburgh and Anderson, 2001).

It is also recognized that the relationship between serum FSH and inhibin B is modulated by other factors. Several
studies have shown that inhibin B levels fall markedly following severe testicular insults (chemotherapy, irradiation) correlating with the disappearance of germ cells (Wallace et al., 1997; Foppiani et al., 1999; Petersen et al., 1999). Similar findings have been observed in rats following methoxyacetic acid treatment (Allenby et al., 1991). On the other hand, gonadotrophic suppression following exogenous sex steroid administration led to little or only a partial suppression of serum inhibin levels (Anderson et al., 1997; Zhengwei et al., 1998; Buchter et al., 1999; Martin et al., 2000; McLachlan et al., 2002) with no relationship with either the duration of treatment or the extent of suppression of sperm count (Anderson et al., 1997). The basis for this differential effect may be that the extent of inhibin B suppression is related to the degree of damage to the spermatogenic process with toxic agents leading to a more profound loss of germ cells, compared with that achieved with gonadotrophin suppression.

To examine the potential influence of germ cells on inhibin release from the testis (of both Sertoli and Leydig cell origin) we examined the acute effects of FSH and/or LH (using hCG as an LH substitute) administration on serum inhibin B and pro-aC levels in normal men, and compared this response with that seen following spermatogenic suppression induced by a regimen developed for the purpose of hormonal contraception (Handelsman et al., 1996). In addition we wished to examine the relationships between spermatogenic recovery, induced by FSH and/or hCG treatment, and serum inhibin B.

Methods and materials

Subjects

Twenty-five healthy men were recruited through media advertisement to participate in this study conducted at Prince Henry’s Institute of Medical Research in accordance with the guidelines of the Southern Healthcare Network Human Research Ethics Committee. Of these 25 men, 15 were enrolled to participate in both the suppression and recovery phases. All men underwent medical interview, physical examination and biochemical investigations. Subjects were required to fulfil each of the following criteria: (i) age 21–45 years, (ii) normal physical findings and normal testicular volumes, (iii) two normal semen analyses (World Health Organization, 1999); (iv) normal serum testosterone, sex hormone-binding globulin, FSH, LH, prolactin and estradiol levels, (v) normal liver and renal function, serum lipids and full blood examination. Men with a past history of hypertension, significant cardiovascular, renal, hepatic, prostatic and testicular disease or infertility were excluded. Men with a past history of drug abuse or who were taking significant prescribed medications were also excluded, as were men undertaking competitive sport who were subject to testing for androgen usage. Informed consent was obtained from all participants.

Study design

Phase 1: Responses of serum inhibin B and pro-aC to single dose gonadotrophin administration. Development of stimulation test protocol. Stimulation test 1

The overall study design is displayed in Figure 1. Twenty-five men were randomized into five groups (n = 5/group) to receive a single injection of one of the following: rhFSH (either Gonal-F, Serono, Sydney, Australia; or Puregon, Organon, Sydney, Australia) 600, 1200, 2400 IU s.c.; hCG (Profasi, Serono; or Pregnyl, Organon) 5000 IU s.c.; or FSH 1200 IU plus hCG 5000 IU. Blood was drawn (0800–1100 h) daily for 8 days beginning on the day prior to the injections in order to cover the likely period of inhibin rise (Anawalt et al., 1996).

Phases 2 and 3: Effects of spermatogenic suppression and recovery on serum inhibin B and pro-aC responses to exogenous gonadotrophins. Stimulation tests 2 and 3

After an interval of ≥6 weeks, 15 men went on to be randomized into three groups (n = 5/group). All men initially received an 800 mg testosterone implant (4×200 mg subdermal, Organon) and depot medroxyprogesterone acetate (DMPA) 300 mg i.m. (2 ml at 150 mg/ml, Upjohn Pharmaceuticals, Sydney, Australia). Following a 12 week suppression phase, all men received a second dose of DMPA (150 mg) to ensure continued gonadotrophin suppression during a further 12 weeks of recovery treatment with either FSH (300 IU twice weekly s.c.) alone, hCG alone (5000 IU weekly s.c.) or a combination of both. Those men receiving only FSH also received a second 800 mg testosterone implant at the beginning of the restoration phase in order to maintain androgen levels in the normal range for the duration of the 12 week-induced recovery period.

For assessing the stimulatory response of serum inhibin, single doses of 1200 IU FSH alone or 5000 IU hCG or a combination of the two were administered by the investigators on day 0 in weeks 1 and 3 of the recovery phase. These doses were chosen based on the data from phase 1 with blood being obtained for each stimulation test on days 0, 4, 5 and 6. The
control response (stimulation test 1) was used for comparison with those obtained after spermatogenic suppression (stimulation test 2) and week 3 in recovery (stimulation test 3). In the remaining weeks of the recovery phase (i.e. 2 and 4–12), men receiving FSH had their FSH doses administered on day 0 by the investigators and self-administered their second FSH dose on day 4 of each week. Men receiving hCG had their dose administered on day 0 of each week by the investigators. Semen analyses and blood samples were obtained weekly throughout the recovery phase.

Baseline characteristics for participants are shown in Table I. Following 12 weeks of gonadotrophin stimulation, men were followed at regular intervals to monitor recovery of FSH, LH and sperm counts.

### Assays

Serum FSH and LH were measured by microparticle enzyme immunoassay (Abbott Diagnostics, North Chicago, Illinois, USA). The sensitivity of the FSH assay was 0.5 IU/l with an inter-assay variation of 4.4–4.9%. The sensitivity of the LH assay was 0.5 IU/l with an inter-assay variation of 5.2–6.4%. Serum FSH and LH were also determined using sensitive immunofluorometric assays (IFMA) (Robertson et al., 2001) with assay sensitivities of 0.01 and 0.005 IU/l for FSH and LH respectively. All samples were assayed in single assays.

Serum hCG was measured in an automated immunoassay carried out on a Dade Behring Dimension RxL Clinical Chemistry system with reagents and calibrators supplied by Dade Behring Diagnostics (Sydney, Australia). The assay sensitivity was 1.0 IU/l with an inter-assay variation of 3.9–6.1%. Testosterone was measured by an automated chemiluminescent immunoassay (Chiron Diagnostics, East Walpole, MA, USA) with a sensitivity of 0.3 nmol/l and inter-assay variations of 5.5–9.9%.

The pro-opC enzyme-linked immunosorbent assay (ELISA) (Groome et al., 1995) was employed using reagents [INPRO monoclonal antibody (Mab) as capture and R1 Mab as label] and a standard reference preparation provided by Oxford Bio-Innovation Ltd (Upper Heyford, Oxon, UK). The sensitivity of the assay was 2 ng/l. The within-assay variation and the between-assay variation were 8±9% and 5±9%. Serum FSH and LH were also determined using sensitive immunofluorometric assays (IFMA) (Robertson et al., 2001) with assay sensitivities of 0.01 and 0.005 IU/l for FSH and LH respectively. All samples were assayed in single assays.

### Statistical analyses

Data are shown as mean ± SEM or mean percentage baseline. Statistical comparisons were made using Sigma Stat (SSPS Inc., Chicago, IL, USA). All data were log-transformed prior to analysis. Non-parametric statistics were used.
when equal variance testing failed. Serum hormone and semen data were analysed by either repeated measures analysis of variance (ANOVA) or Friedman repeated measures ANOVA followed by Tukey test to examine differences across time between treatment groups. Differences in percentage baseline inhibin B (day 0 compared with days 4–6) and pro-αC (day 0 compared with days 4–5) in stimulation tests 1, 2 and 3 in each treatment group was evaluated using one-way ANOVA.

Results

Phase 1

Serum gonadotrophins and testosterone levels
Dose-related increases were seen in serum FSH in response to FSH stimulation (Figure 2A). Serum FSH levels fell significantly over days 2–7 with hCG treatment (*P < 0.001). Serum testosterone increased (*P < 0.05) in FSH plus hCG group compared with hCG-alone group. Note log scale for the y-axis in B. Data are shown as mean ± SEM, n = 5/group.

Serum inhibin B and pro-αC
Serum inhibin B and pro-αC responses to treatments are shown in Figures 3 and 4 with data expressed as percentage of baseline.
Serum FSH and LH levels (Testosterone plus DMPA treatment markedly suppressed serum gonadotrophins and testosterone levels in Phases 2 and 3 (Figure 3B). A profile was seen by co-administration of hCG to 1200 IU FSH (195±198% baseline, Figure 4B). No change in the inhibin B and apparent additive increase in pro-

Figure 4. (A) Changes in serum pro-αC levels in subjects administered a single dose of FSH (600, 1200, 2400 IU). Significant increases were observed between day 0 and days 2–6 (P < 0.05) for FSH 1200 and 2400 IU treatment groups. Data shown as percentage baseline, mean±SEM, n = 5/group. (B) Changes in serum pro-αC levels in subjects administered a single dose of FSH (1200 IU), FSH (1200 IU) plus hCG (5000 IU) or hCG (5000 IU). Pro-αC levels were significantly increased relative to day 0 in the FSH (1200 IU) plus hCG (5000 IU) group between days 1–5 (P < 0.01) and days 6–7 (P < 0.05), and in the hCG (5000 IU) treatment group between days 0 and days 1–2 (P < 0.01) and 3–4 (P < 0.05). Data shown as percentage baseline mean±SEM, n = 5/group.

baseline. Serum inhibin B was significantly increased with 1200 and 2400 IU FSH on days 4–5 (130% of baseline) and 2–7 (138–154% baseline) respectively. Pro-αC levels significantly increased with 1200 and 2400 IU FSH on days 2–6 (140–185% baseline, Figure 4A, B). hCG alone did not affect inhibin B levels but led to a rapid rise in pro-αC by day 1 (145% baseline, Figure 4B). Co-administration of FSH and hCG led to an apparent additive increase in pro-αC levels on days 4–5 (195–198% baseline, Figure 4B). No change in the inhibin B profile was seen by co-administration of hCG to 1200 IU FSH (Figure 3B).

Phases 2 and 3
Serum gonadotrophins and testosterone levels
Testosterone plus DMPA treatment markedly suppressed serum FSH and LH levels (P < 0.05) to the limit of assay detection (only FSH data shown, Figure 5A). Similar peak FSH and hCG levels were seen with stimulation tests 2 (5.4–5.8 and 27.0–28.6 IU/l) and 3 (5.1–5.6 and 31.0–33.5 IU/l) on day 4 (Figure 5A, B). FSH levels measured by the sensitive FSH IFMA in the hCG treatment group were markedly suppressed but remained detectable across the recovery phase with mean levels ranging from 0.025 IU/l (0.79% control baseline) in week 3 to 0.13 IU/l (4% control baseline) by week 7. LH levels determined by the sensitive LH IFMA in the FSH treatment group fell to the limit of the assay (0.005 IU/l, 0.16% control baseline) and remained suppressed for the duration of the study (sensitive assay FSH and LH data not shown). Testosterone levels remained within the physiological range except at some time-points in the FSH-alone-treated group which received a second testosterone implant at the onset of the recovery phase in order to prevent hypogonadism (Figure 1). Co-administration of FSH with hCG as compared with hCG alone appeared to augment the testosterone response with a statistically significant higher testosterone level being seen with FSH plus hCG treatment (P < 0.05) in week 7. Comparison of testosterone levels in the FSH-alone group was not analysed due to the use of a second testosterone implant in this group (Figure 5C).

Serum inhibin B and pro-αC
In all 15 men receiving testosterone plus DMPA treatment for 12 weeks, significant falls (P < 0.001) were seen in both mean serum inhibin B (88.7±13.5 versus 61.6±6.9 ng/l, 75% pre-treatment baseline) and pro-αC levels (34.0±3.4 versus 14.8±1.9 ng/l, 51% pre-treatment baseline). Changes in serum inhibin B and pro-αC for each treatment group are shown as a percentage of pre-treatment levels (Figure 6A, B). Inhibin B levels declined significantly with hCG stimulation to a nadir by week 3, day 5 (41% pre-treatment baseline, P < 0.001). On the other hand, FSH alone and FSH plus hCG led to a prompt increase in serum inhibin B levels (Figure 6A). All treatments led to a rise in serum pro-αC (Figure 6B).

Inhibin B and pro-αC responses to gonadotrophic stimulation following spermatogenic suppression (stimulation test 2) and week 3 in recovery (stimulation test 3) are shown in Figure 7A, B. Inhibin B and pro-αC, day 0 test values in each stimulation test were used for assessment of the gonadotrophic response. In stimulation test 2, only FSH-alone treatment led to a significant rise in inhibin B by day 5 (144%, P = 0.038). Pro-αC was significantly raised over days 4–6 with both hCG (254–261%, P < 0.001) FSH-alone (210–229%, P < 0.001) and treatments thereafter remaining stable. Combined FSH plus hCG treatment also resulted in an increase in pro-αC although not reaching significance. In stimulation test 3, no significant changes in either inhibin B or pro-αC levels were seen for any treatment group.

Comparison of the gonadotrophin stimulatory responses of serum inhibin B (days 4–6) and pro-αC (days 4–5) were calculated using the baseline day 0 value for each of the three stimulation tests. Administration of hCG alone had no stimulatory effect on inhibin B at any time-point. Pro-αC responses to hCG (119±10 versus 279±53 versus 127±31%) and FSH (158±21 versus 225±20 versus 113±10%) stimulation were significantly (P < 0.05) greater following spermatogenic suppression (stimulation test 2) compared
with control (stimulation test 1) and week 3 in induced recovery (stimulation test 3).

**Spermatogenic suppression and recovery**

Testosterone plus DMPA treatment led to marked suppression of spermatogenesis (0.08–0.21×10⁶/ml) in all 15 men (Figure 6C). All recovery treatments led to a partial restoration in spermatogenesis with sperm counts in the hCG group ranging from 0.21 to 8.4×10⁶/ml, in the FSH group between 0.07 and 10×10⁶/ml and in the combined group between 0.21 and 69×10⁶/ml. However, despite all groups showing partial restoration of spermatogenesis, serum inhibin B levels either fell with hCG, or returned toward control levels with FSH alone or combined with hCG. No clear relationship was apparent between serum inhibin B levels and sperm counts over the 12 week-induced recovery phase (Figure 6A, C).
Three men required additional testosterone replacement and testosterone levels recovered in all 14 men between 1 and 12 months. Recovery and adverse events

Recovery to pre-study baseline was monitored in 13 of the 15 participants, one of the subjects in the FSH plus hCG group. Two participants in the suppression phase developed mild gynaecomastia, one transiently, the other having persistent 1 cm non-tender unilateral enlargement. No other serious adverse events occurred.

Discussion

This study has investigated the serum inhibin B and pro-αC responses of the normal testis to gonadotrophin stimulation, and is the first to explore the impact of the suppression of germ cell number on their release. We have shown that the suppression of spermatogenic cells does not modify the acute inhibin B response to FSH. Indeed serum inhibin B appears to be a poor marker of spermatogenesis in this model of experimental gonadotrophic manipulation. Only a 25% decline in serum inhibin B was observed even when germ cell numbers were markedly reduced, resulting in severe oligo- or azoospermia (McLachlan et al., 2002), and serum FSH levels were suppressed to <4% of baseline levels. In terms of the maximal inhibin B secretory response of the normal testis to gonadotrophin treatment, only an ~40% increase over baseline was seen and this increment was not modified by spermatogenic suppression. Others have also shown that inhibin B levels are only partially FSH dependent (Anawalt et al., 1996; Nachtigall et al., 1996; Seminara et al., 1996; Anderson et al., 1997; Buchter et al., 1999; Martin et al., 2000).

There is considerable evidence that germ cells modify inhibin responses in both animal (Pineau et al., 1989, 1990; Maddocks et al., 1992) and human models (Carreau, 1995; Andersson et al., 1998). The mechanism of this effect is unclear but germ cells may regulate the synthesis and incorporation of the βB subunit into dimeric inhibin by the Sertoli cell, the rate-limiting step in inhibin B synthesis (Clifton et al., 2002).

In normal men, a positive relationship is recognized between serum inhibin and sperm output (Jensen et al., 1997; Klingmuller and Haidl, 1997). Therefore in our model of spermatogenic suppression in normal men, one could postulate several possible impacts of germ cells on the Sertoli cell inhibin B secretory response. The most likely relationship would be that germ cells potentiate the ability of the Sertoli cell to secrete inhibin B, resulting in decreased secretion in the setting of germ cell depletion. Alternatively, if germ cells inhibit Sertoli cell inhibin B secretion, then in the setting of germ cell depletion, there may be an increase in its secretion, either basally or in response to FSH. Finally if there are non-germ cell factors modulating the ability of the Sertoli cell to secrete inhibin B, then there may be no significant change in Sertoli cell inhibin B response.

We have shown that the combined reduction in germ cell number and suppression of gonadotrophins resulted in significant falls in inhibin B and pro-αC. However, germ cell depletion in normal young men did not modify the ability of the Sertoli cell inhibin B response to gonadotrophins. Comparison of the inhibin B response with FSH showed no significant differences between control (stimulation test 1) and following germ cell suppression (stimulation test 2).
The hypothesis that specific germ cell types might regulate inhibin in normal men (Pineau et al., 1990; Allenby et al., 1991; Guitton et al., 2000; Clifton et al., 2002) is difficult, if not impossible, to assess as specific and complete loss of germ cell subtypes cannot be achieved. Germ cell types are suppressed to a variable degree by chronic gonadotrophin suppression in man (McLachlan et al., 2002). Type A and B spermatogonia were suppressed to ~70 and ~20% of control levels respectively, with spermatocytes, round and elongated spermatids remaining at 20%, indicating that the type A pale to B spermatogonial maturation is the key site of effect. The reduction of sperm counts to levels <1% of control is in large part attributed to the failure of sperm release (McLachlan et al., 2002). In contrast, iatrogenic spermatogenic failure, e.g. by cancer treatments, generally induces total spermatogenic failure, although these treatments may also alter Sertoli/Leydig cell function and interaction.

Alteration in Sertoli cell inhibin secretion in our model could also have resulted from either a chronic FSH deficiency modifying the ability of the Sertoli cells to respond to acute FSH stimulation and/or to the effect of changes in the germ cell complement. We attempted to address this issue by repeating the stimulation test in week 3 of FSH-induced recovery, by which time we speculated that any FSH-related defect in Sertoli cell function would have been corrected and that there would still be a low germ cell complement. However, there was no suggestion of a 'priming effect' of FSH treatment leading to an increased inhibin B response in the third week.

An FSH dose–response effect on pro-αC secretion was seen, with ≥1200 IU FSH being required for a maximal response. The rise in pro-αC after hCG was more rapid (peak day 1–2) than with FSH, suggesting that the Leydig cell responds more rapidly to its tropic hormone than does the FSH–Sertoli cell axis. Additive effects of FSH and hCG on pro-αC were seen in both the single dose acute setting and during recovery, implying that both the Sertoli and Leydig cells contribute during combined treatment. This would also be in keeping with immunohistochemical data which have shown α-subunit staining in both Sertoli and Leydig cells (Bergh and Cajander, 1990; Forti et al., 1992; Vannelli et al., 1992; Majdic et al., 1997; Anderson et al., 1998; Andersson et al., 1998). As previously shown, hCG (as an LH substitute) does not stimulate inhibin B secretion (Kamischke et al., 2001; Kinniburgh and Anderson, 2001).

In contrast with the inhibin B response, germ cell loss appeared to enhance pro-αC responses to both FSH and hCG. It is possible that germ cells may have an inhibitory effect on the production of the α-subunit by both the Sertoli and Leydig cells which, when removed, results in a greater secretion of this isoform. Equally possible is that the germ cells positively influence the production of the βB-subunit by the Sertoli cell to FSH and that their removal results in less dimerization and thus an apparent increase in the free α-subunit. However, this apparent increase in pro-αC may also relate to the lower baseline value for the test after gonadotrophin suppression (stimulation test 2). It should also be noted that there was a lesser pro-αC response with the presumed return of germ cells in the third week of recovery. In any event, it is clear that both Sertoli (FSH-dependent) and Leydig cell (hCG/LH-dependent) components respond more vigorously in terms of pro-αC secretion than inhibin B with germ cell depletion.

Germ cell/FSH/inhibin relationships may differ in other settings of testicular dysfunction. Despite severe germ cell depletion, high levels of α-subunit-containing peptides are found in infertile men, including Klinefelter’s syndrome (Anawalt et al., 1996), and chemotherapy-induced azoospernia (Wallace et al., 1997), in which settings, inhibin B levels are very low or undetectable. This observation of pro-αC is gonadotrophin sensitive as suppression of FSH/LH reduces the serum levels (Martin et al., 2000; Kinniburgh et al., 2002). The threshold for FSH and LH/hCG effects on both inhibin B and pro-αC may differ in these disease settings compared with those in the current study. The rise in pro-αC in male infertility may result from the much more severe loss of germ cell number (e.g. Sertoli cell-only syndrome) than that seen in our model, resulting in increased α-subunit secretion, and/or a loss of inhibin B secretory capacity. It has been previously suggested (Wallace et al., 1997) that observed differences could be accounted for by the frequently elevated serum LH levels in these subjects leading to an increased secretion of α subunit by the Leydig cell. However, it is also possible that there is a contribution by preferential secretion of α-subunit by the Sertoli cell in the face of severe germ cell loss and high FSH levels.

One interesting incidental finding was the augmentation of hCG-induced testosterone secretion associated with co-administration of FSH, both in the single dose acute setting and over the weeks of recovery. These data support the previous observation (Levalle et al., 1998) that enhancement of Sertoli cell function by FSH stimulation may result in improved Leydig cell function via paracrine effects. Given that there are no FSH receptors on Leydig cells, it has been suggested that the increase in testosterone observed after the administration by FSH is possibly mediated via a Sertoli cell released non-steroidal factor with a molecular mass of >50 kDa (Levalle et al., 1998). However, this effect was not seen in subjects with acquired hypogonadotropic hypogonadism in whom no further rise in serum testosterone was seen following 1 month of treatment with FSH with or without hCG (Young et al., 2000). One potential explanation for these differences is that in the latter study, testicular size was markedly reduced (4–10 ml) probably due to spermatogenic failure. In turn this may have altered Sertoli cell function and its ability to augment Leydig cell testosterone secretion which was not restored by 1 month of gonadotrophin treatment.

In conclusion, we found that inhibin B in this setting of experimental germ cell depletion in normal men is a poor marker of spermatogenesis, as germ cell loss led to only minor changes in basal inhibin B levels and no modulation of FSH stimulatory response. Furthermore, during induced gonadotrophin recovery of spermatogenesis, no clear relationship was seen between sperm output and serum inhibin B. However, we caution that this conclusion should not be extrapolated to other settings of genetic or acquired defects of spermatogenesis.
wherein different FSH/inhibin B/spermatogenic relationships may exist and account for the observed reciprocal relationship between serum inhibin B and FSH in spermatogenic failure.

Thus, while we see no benefit in the use of an FSH stimulation test to assess spermatogenic status in normal men, it may be useful in some settings of male infertility.

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References


Gonadotrophin stimulation of inhibin


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