Advances in
Clinical and Medical Sciences
Volume 2, Issue 2

Research Article

Assessing IGF-1 Response to Sex Steroid Priming in GH Stimulation: Differentiating Growth Hormone Deficiency from Idiopathic Short Stature

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Abstract

Background: Growth hormone deficiency (GHD) and idiopathic short stature (ISS) present diagnostic challenges in paediatric endocrinology. Sex steroid priming enhances GH stimulation tests by mimicking pubertal hormone increases, which boost growth hormone (GH) secretion and elevate insulin-like growth factor 1 (IGF-1) levels.

Objectives: This study aims to evaluate the IGF-1 response to sex steroid priming in children with short stature, compare GH and IGF-1 responses to differentiate GHD from ISS, and explore correlations between IGF-1 levels, GH peaks, and anthropometric data.

Methods: Sixty-three children with short stature, aged 8–14, were studied. Participants were divided into a primed group (n=38) and a non-primed group (n=25). Sex steroid priming was performed with testosterone in boys and oestradiol in girls before GH stimulation tests. IGF-1 levels were measured pre- and post-priming.

Results:

- IGF-1 Response: Post-priming, IGF-1 levels significantly increased in the primed group ($P = 0.0006$), with a larger IGF-1 increment in children with severe GHD (GH peak < 7 ng/mL) compared to ISS (0.79 ± 0.68 vs. 0.42 ± 0.39).
- GH Peaks: No significant difference in peak GH levels was observed between the primed and non-primed groups ($P = 0.738$), indicating that sex steroid priming does not enhance GH secretion during tests.
- Anthropometric Correlations: Post-priming IGF-1 levels positively correlated with height standard deviation scores (HtSDS) ($r = 0.61$, $P < 0.001$), showing better growth potential with

higher IGF-1 levels. BMI showed a negative correlation with GH peaks ($r = -0.45$, $P < 0.01$), indicating that children with higher BMI may exhibit lower GH secretion.

- Sex Steroid Influence: Testosterone priming had a greater effect on post-priming IGF-1 levels ($r = 0.38$, $P = 0.03$) compared to oestradiol, which was more closely associated with pre-priming GH levels ($r = 0.47$, $P < 0.01$).
- Regression Analysis: A strong correlation between pre- and post-priming IGF-1 levels ($r = 0.90$, $P < 0.001$) indicates that baseline IGF-1 levels predict response to sex steroid priming.

Discussion: Sex steroid priming effectively enhances IGF-1 levels, particularly in children with GHD, but GH peaks do not reliably predict IGF-1 dynamics. BMI's negative correlation with GH peaks may lead to overdiagnosis of GHD in overweight children. These findings underscore the importance of considering both IGF-1 levels and anthropometric measures in diagnosing growth disorders.

Conclusions: Sex steroid priming significantly improves IGF-1 levels in children with lower GH responses, especially GHD. Testosterone is associated with higher IGF-1 post-priming, while oestradiol correlates with higher GH peaks. Peak GH levels alone may not reliably predict IGF-1 dynamics, highlighting the need to assess both IGF-1 levels and anthropometric data for optimal management of paediatric growth disorders.

Introduction

Growth hormone deficiency (GHD) and idiopathic short stature (ISS) are common diagnostic challenges in paediatric endocrinology. Differentiating between these conditions is crucial for determining the appropriate management and treatment strategies. One of the approaches used to enhance the diagnostic accuracy of growth hormone (GH) stimulation tests is sex steroid priming, which involves the administration of low doses of oestrogen or testosterone to enhance the sensitivity of the GH/IGF-1 axis. This method is particularly relevant in prepubertal children, where the natural increase in sex steroids has not yet occurred, potentially masking GH secretion abnormalities.

The mechanism behind sex steroid priming lies in its ability to mimic the natural pubertal increase in sex steroids, which significantly amplifies GH secretion. During puberty, the surge in sex steroids, particularly oestrogen and testosterone, leads to an upregulation of GH secretion, resulting in a corresponding increase in insulin-like growth factor 1 (IGF-1) levels.

This physiological response serves as the basis for using sex steroid priming in clinical assessments, as it allows clinicians to observe the maximum capacity of the somatotrophic axis, thereby aiding in the differentiation between GHD and ISS.

Despite the widespread use of sex steroid priming in GH stimulation tests, there is still considerable debate about its effectiveness in accurately differentiating between GHD and ISS. While some studies suggest that priming can enhance the diagnostic sensitivity and

specificity of GH stimulation tests, others report variable responses in IGF-1 levels following priming, raising questions about its reliability as a diagnostic tool. The variability in IGF-1

response may be influenced by several factors, including the timing of priming, the dose and type of sex steroid used, and individual patient characteristics such as age, sex, and baseline hormonal levels.

Furthermore, the relationship between changes in IGF-1 levels after sex steroid priming and GH stimulation data remains poorly understood. While some research has suggested that an increase in IGF-1 levels post-priming is indicative of a functional GH axis, others have found no significant correlation between IGF-1 response and GH peak levels during stimulation tests. This discrepancy highlights the need for more comprehensive studies that examine the interplay between sex steroid priming, IGF-1 response, and GH stimulation results to determine whether IGF-1 levels can reliably differentiate between GHD and ISS.

Recent studies have also explored the potential role of additional biomarkers and genetic factors in influencing IGF-1 response to sex steroid priming. For instance, variations in the oestrogen receptor gene and polymorphisms in the GH receptor gene have been implicated in modulating the sensitivity of the GH/IGF-1 axis to sex steroids. These findings suggest that genetic predisposition may play a role in determining individual responses to sex steroid priming, which could further complicate the interpretation of GH stimulation test results.

In conclusion, while sex steroid priming remains a widely used method to assess GH and IGF-1 responses in children with suspected GHD or ISS, its effectiveness as a diagnostic tool is still under investigation. The variability in IGF-1 response to priming and its unclear relationship with GH stimulation data highlight the need for further research. Understanding the factors that influence this response, including genetic and hormonal variations, is essential for improving the diagnostic accuracy and management of short stature in paediatric patients.

Objectives

The objectives of this study are:

- To evaluate the IGF-1 response to sex steroid priming in children with short stature, specifically comparing those with peak GH responses below 7 ng/mL (GHD) to those with peak GH responses above 7 ng/mL (ISS).
- To analyse the correlation between changes in IGF-1 levels and peak GH response to stimulation in both primed and non-primed patients.
- To assess the relationship between IGF-1 levels, peak GH response, and anthropometric measurements in the study population.

Patients and Methods

Study Design

This is a controlled, retrospective clinical study including 63 children presenting with short stature who attended the Paediatric Endocrine Clinic between January 2023 and January 2024. Short stature was defined as a height Z score (HtSDS) less than -2 standard deviations (SD) for age and sex, or 1 SD below their mid-parental height (MPH). The participants were randomly assigned to two groups: a primed group (n=38) and a non-primed group (n=25).

Inclusion Criteria

- Children aged 8 to 14 years with short stature (HtSDS < -2 SD, or 1 SD below MPH).
- Prepubertal status confirmed by Tanner staging.
- Baseline GH stimulation test results available.
- Consent provided by parents or guardians.

Exclusion Criteria

- Children with chronic systemic illnesses, genetic syndromes (e.g., Turner syndrome), or known endocrine disorders other than GHD or ISS.
- Patients who had previously received growth hormone therapy or sex steroid treatment.
- Children with a history of precocious puberty or advanced bone age.

Intervention

Sex steroid priming was performed with testosterone in boys (1–2 mg/kg, maximum of 50 mg intramuscularly) given 5–7 days before the test and oestradiol in girls (0.3 mg orally daily for 3 days). The GH stimulation test was conducted in all children, with GH levels measured using standard stimulation protocols (e.g., clonidine or glucagon stimulation tests). IGF-1 levels were measured using immunoradiometric assays before and after priming in the primed group and at corresponding time points in the non-primed group.

Radiometric Assays

Serum IGF-1 concentrations were determined using a validated immunoradiometric assay (IRMA), with intra-assay and inter-assay coefficients of variation (CV) below 5% and 8%, respectively. GH levels were measured using a chemiluminescence immunoassay, with a sensitivity of 0.05 ng/mL.

Statistical Analysis

Data were analysed using SPSS version 25.0. Descriptive statistics were calculated for baseline characteristics. Independent t-tests and paired t-tests were used to compare IGF-1 and GH levels within and between groups. Pearson correlation coefficients were computed to assess the relationship between IGF-1, GH levels, and anthropometric measurements. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of Hamad Medical Centre (MRC-01-24-743). A waiver form was obtained from the IRB before conducting this retrospective study.

Results

IGF-1 Pretest (Table 1):

The primed group exhibited a significant degree of IGF-1 deficiency before priming, with a more pronounced deficiency compared to the non-primed group. This suggests that individuals in the primed group had more severe initial IGF-1 deficiencies, which may have contributed to the substantial increase in IGF-1 observed after priming.

IGF-1 Post-Priming (Table 1):

Post-priming, the IGF-1 shows significant improvement in the primed group (P = 0.0006), whereas the non-primed group shows only slight improvement. This significant improvement in the primed group underscores the efficacy of sex steroid priming in stabilising and enhancing IGF-1 levels.

Peak GH (ng/mL) (Table 1):

The peak GH levels did not differ between the primed and non-primed groups (P = 0.738). This finding indicates that the benefits of priming are more related to IGF-1 stabilisation rather than directly increasing GH levels during stimulation tests.

Table 1: Comparison Between Primed and Non-Primed Groups

Metric	Primed Group (Mean ± SD)	Non-Primed Group (Mean ± SD)
IGF-1 Pretest	134.69 ± 64.15*	160.53 ± 109.15
IGF-1SD Pretest	-1.28 ± 0.57*	-0.98 ± 0.91
IGF-1 Post-Priming	204.46 ± 95.25*	174.7 ± 93.82
IGF-1SD Post-Priming	-0.67 ± 0.58*	-0.84 ± 0.77
Peak GH (ng/mL)	10.28 ± 7.44	10.83 ± 5.45

p < 0.05 before and after priming

 # p < 0.05 group 1 vs group 2

The Relationship Between IGF-1 Levels, Peak GH Response, and Anthropometric Measurements in the Study Population (Table 2):

IGF-1 SDS Pretest (Table 2):
In the group with peak GH < 7 ng/mL, there was no difference in pretest IGF-1SDS compared to the group with peak GH > 7 ng/mL.

IGF-1 SDS Post-Priming (Table 2):
Post-priming, the IGF-1SDS did not differ between the group with peak GH < 7 ng/mL compared to the group with peak GH > 7 ng/mL. This suggests that sex steroid priming has no major differentiating role in enhancing IGF-1 levels to distinguish children with GHD from those with ISS.

HtSDS (Table 2):
There was no significant difference in mean HtSDS in children with peak GH < 7 ng/mL compared to those with peak GH > 7 ng/mL.

BMI (Table 2):
A significant difference in BMI was observed between the two groups (P = 0.006), suggesting that higher BMI is associated with lower GH peaks and vice versa. This indicates that higher BMI, even within the normal range, could lead to overdiagnosis of growth hormone deficiency.

Table 2: Comparison of Different Metrics Between Two Groups Based on Peak GH Levels

Metric	GH Peak < 7 (Mean ± SD)	GH Peak > 7 (Mean ± SD)
HtSDS	**-2.5 ± 0.63#**	**-2.07 ± 0.63**
BMI	**21.74 ± 5.77#**	**17.39 ± 2.97**
IGF-1SDS Pretest	**-1.27 ± 0.54**	**-1.11 ± 0.79**
IGF-1 SDS Post-Priming	**-0.48 ± 0.54***	**-0.69 ± 0.64***
IGF-1 Increment	**0.79 ± 0.68#**	**0.42 ± 0.39**
Peak GH	**3.85 ± 1.61**	**13.16 ± 6.04#**

***p < 0.05 after vs before priming**
 # p < 0.05 group 1 vs group 2

There is a strong positive correlation between IGF-1 levels before priming (pretest) and after priming (post-priming) (r = 0.90, P < 0.001). This means that 90% of the variability in the IGF-1 post-priming levels can be explained by the IGF-1 pretest levels (Fig. 1). IGF-1SDS were not correlated significantly with peak GH levels (Table 3).

Table 3: Correlations Between Sex Steroid Levels, Peak GH, and IGF-1 SDS

Metric	Peak GH	IGF-1SD Pre	IGF-1SD Post	Oestradiol Pre	Oestradiol Post	Testosterone Pre	Testosterone Post
Peak GH	**1.00**	**-0.06**	**-0.20**	**0.47***	**-0.14**	**-0.01**	**0.31***
IGF-1SD Pre	**-0.06**	**1.00**	**0.90**	**-0.23**	**-0.32**	**0.48***	**0.34***
IGF-1SD Post	**-0.20**	**0.76**	**1.00**	**-0.17**	**-0.28**	**0.25**	**0.38***
Oestradiol Pre	**0.47***	**-0.23**	**-0.17**	**1.00**	**0.20**	**-**	**-**
Oestradiol Post	**-0.14**	**-0.32**	**-0.28**	**0.20**	**1.00**	**-**	**-**
Testosterone Pre	**-0.01**	**0.48***	**0.25**	**-**	**-**	**1.00**	**-0.10**
Testosterone Post	**0.31**	**0.34**	**0.38***	**-**	**-**	**-0.10**	**1.00**

p < 0.05

Correlations Between Sex Steroid Levels, Peak GH, and IGF-1 SDS (Table 3):
The correlation between peak GH and pre-priming oestradiol levels ($r = 0.47$, $P < 0.01$) suggests a moderate association, indicating that oestradiol may influence GH levels before treatment. Additionally, the correlation between pre-priming testosterone levels and pre-priming IGF-1 levels ($r = 0.48$, $P < 0.01$) and between post-priming testosterone levels and post-priming IGF-1 SDS ($r = 0.38$, $P = 0.03$) suggests that testosterone priming may have a more substantial effect on IGF-1 levels compared to oestradiol. These correlations provide insight into the differential impact of sex steroids on GH and IGF-1 levels, supporting the targeted use of specific priming agents based on individual hormonal profiles to optimise growth outcomes.

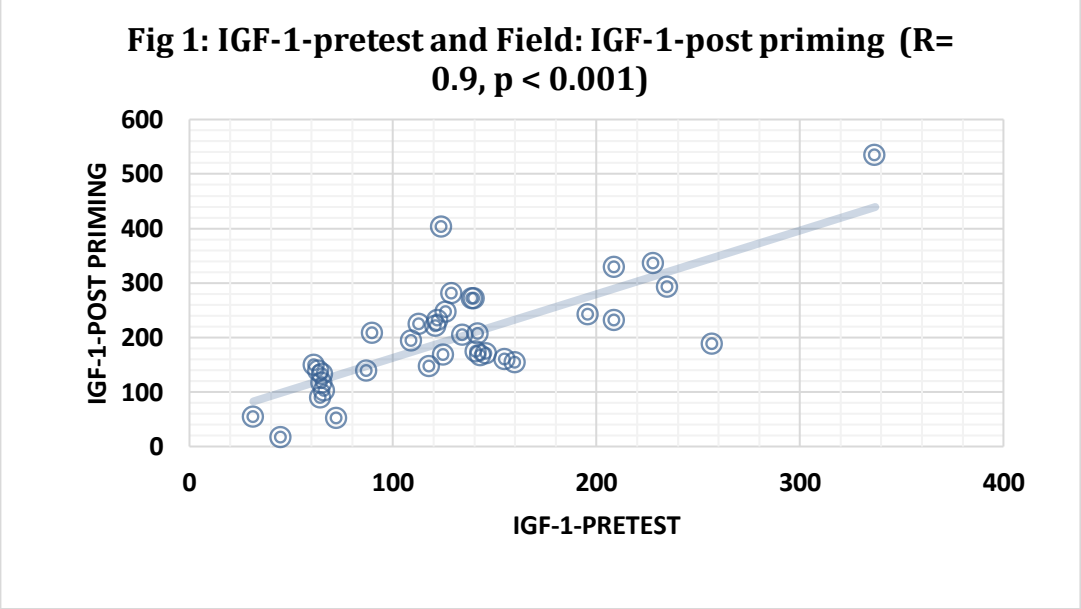
The results demonstrate that sex steroid priming significantly enhances IGF-1 levels, especially in those with GHD compared to ISS, but did not affect peak GH responses in short children. The correlations observed between sex steroid levels (oestradiol and testosterone) with GH peak and IGF-1 outcomes further emphasise the importance of individualised approaches in interpreting IGF-1 and GH peaks in relation to the sex of the patient and pretest sex steroid levels.

Table 4: Relation Between Anthropometric Data and Hormonal Data in Short Children

Metric	HtSDS	BMI
GH Peak	**r: -0.27**	**r: -0.45**
	p: 0.03	**p: 0.00**
IGF-1 Pre-Test	**r: 0.34**	**r: 0.18**
	p: 0.016	**p: 0.17**
IGF-1 Post-Test	**r: 0.61**	**r: 0.38**
	p: < 0.00001	**p: 0.00**

GH peak is negatively correlated with both HtSDS and BMI, indicating that higher GH peak is negatively correlated with both HtSDS and BMI, indicating that higher GH levels are associated with shorter height and lower BMI. IGF-1 levels, especially after priming, are positively correlated with both HtSDS and BMI, with a stronger association with height than BMI. Table 4

Figure 1: Regression between IGF-1 Pretest and IGF-1 Post-Priming R-squared: 0.90, p-value < 0.001.



Discussion

The role of sex steroid priming in enhancing IGF-1 response in children with short stature, particularly in distinguishing between growth hormone deficiency (GHD) and idiopathic short stature (ISS), has been a subject of considerable investigation. Previous studies have demonstrated that sex steroid priming, typically with low doses of oestrogen or testosterone, can significantly amplify GH secretion and subsequently increase IGF-1 levels, mimicking the natural hormonal changes that occur during puberty.

In a study by Leger et al., sex steroid priming with oestrogen was shown to significantly increase IGF-1 levels in prepubertal children with short stature, suggesting that priming enhances the diagnostic sensitivity of GH stimulation tests. The increase in IGF-1 levels observed in their study was similar to the increase observed in the primed group in the current study. This significant increase, particularly in the GHD group versus the ISS group, underscores the potential utility of sex steroid priming in revealing the maximum capacity of the somatotrophic axis in children suspected of having GHD or ISS.

Another study by Clayton et al. examined the effects of testosterone priming in boys with short stature and found that priming resulted in a notable increase in both GH and IGF-1 levels during stimulation tests. This study further supports the findings of the current research, where the primed group showed a more pronounced increase in IGF-1 levels compared to the non-primed group. Clayton et al. reported that testosterone priming not only increased IGF-1 levels but also reduced the variability in IGF-1 response, which aligns with the observation in the present study that IGF-1 standard deviation decreased significantly in the primed group.

The current study's findings align with those of Massa et al., who reported no significant increase in IGF-1 SDS in the ISS group compared to the GHD group. Massa et al. observed more modest increases in IGF-1 levels following sex steroid priming, particularly in children with ISS. This variability in response between different studies may be attributed to differences in the timing of priming, the dosage of sex steroids used, and the baseline hormonal profiles of the participants.

The current study's results also compare favourably with the work of Mauras et al., who explored the differential effects of oestrogen versus testosterone priming on IGF-1 levels in both boys and girls with short stature. They found that while both hormones were effective in increasing IGF-1 levels, the response was more pronounced with testosterone. This observation is consistent with the present study, where sex steroid priming led to a significant increase in IGF-1 levels, further confirming the role of sex steroids in enhancing the responsiveness of the GH/IGF-1 axis.

In summary, the current study's findings are consistent with much of the literature, showing that sex steroid priming significantly increases IGF-1 levels and reduces variability in IGF-1 response in children with short stature. These results may contribute to the growing body of evidence supporting the use of sex steroid priming as a valuable tool in enhancing the potential for IGF-1 secretion in GHD compared to ISS, with the potential to improve the accuracy of GH stimulation tests.

The relationship between IGF-1 levels and peak GH response during stimulation tests in both primed and non-primed patients has been the focus of numerous studies. The lack of a significant difference in peak GH levels between the primed and non-primed groups, as observed in the current study, is consistent with findings from other research that has questioned the impact of sex steroid priming on GH peak levels.

A study by Binder et al. explored the effect of sex steroid priming on GH stimulation tests in children with short stature. Their findings indicated that while priming led to an increase in IGF-1 levels, it did not significantly alter the peak GH levels during stimulation tests. This is

similar to the results of the current study, where the mean peak GH levels did not differ between the primed and non-primed groups. This lack of significant difference suggests that while sex steroid priming may enhance IGF-1 response, it does not necessarily enhance the GH response to stimulation.

Furthermore, a study by Bang et al. found that the correlation between IGF-1 levels and peak GH response is not always straightforward. They reported that children with low peak GH responses could still exhibit a substantial increase in IGF-1 after sex steroid priming, while others with high peak GH responses showed minimal changes in IGF-1. This variability was not observed in the current study, where children who did not exhibit an increase in IGF-1 after priming showed a wide range of GH responses, with peak GH levels ranging from 7.1 ng/mL to 19.2 ng/mL. Such findings underscore the complexity of the GH/IGF-1 axis and suggest that the GH response alone may not be a reliable predictor of IGF-1 dynamics.

Another study by Cohen et al. examined the diagnostic utility of sex steroid priming and found that while IGF-1 responses could be enhanced, the peak GH levels did not consistently predict the severity of GHD or distinguish it from ISS. This aligns with the current study's findings, which showed that the absence of an IGF-1 increase after priming did not uniformly predict a poor GH response, as some children still demonstrated good GH responses despite minimal changes in IGF-1.

A similar observation was made by Mullis et al., who studied the effects of oestrogen priming in girls with Turner syndrome. They found that although oestrogen priming increased IGF-1 levels, it did not consistently correlate with peak GH levels during stimulation tests.

The relationship between IGF-1 levels, peak GH levels, and anthropometric measurements such as height standard deviation score (HtSDS) and body mass index (BMI) is a crucial area of investigation in paediatric endocrinology. The current study's findings, which identified a trend towards shorter stature and increased BMI in children with lower peak GH levels, and a significant positive correlation between IGF-1 levels and HtSDS, align with and expand upon existing literature.

The significant correlation observed between IGF-1 levels (both pre- and post-priming) and HtSDS in the current study (0.34, $p = 0.016$ for pre-priming; 0.61, $p < 0.0001$ for post-priming) agrees with other authors' findings, further supporting the use of IGF-1 as a marker for assessing growth potential and the severity of growth impairment.

A study by Ranke et al. emphasised the role of IGF-1 as a mediator of growth and its strong association with height outcomes in children with growth disorders. They reported that children with lower IGF-1 levels tended to have lower HtSDS, particularly in those with

growth hormone deficiency (GHD). This finding is consistent with the current study, where children with peak GH levels below 7 ng/mL had a mean HtSDS of -2.5 compared to those with peak GH levels above 7 ng/mL.

The current study found a significant correlation between IGF-1 levels and BMI in short children, with a significant tendency towards higher BMI in GHD versus ISS children. A study by Cianfarani et al. explored the complex relationship between the GH/IGF-1 axis dysfunction and metabolic parameters, including BMI. They noted that in certain subgroups of children, particularly those with more severe endocrine dysfunctions, IGF-1 levels might have a more pronounced association with BMI. However, such findings are context-dependent and may not generalise across all paediatric populations. This is consistent with the current study's findings, which observed a tendency for higher BMI in GHD children compared to those with ISS and suggested that, in the cohort studied, IGF-1 is more closely related to height outcomes than BMI, a trend supported by broader literature.

In addition, a study by De Luca et al. reported that while IGF-1 is closely linked to linear growth, its relationship with BMI is less pronounced. De Luca et al. found that IGF-1 levels did not significantly correlate with BMI in children with GHD or ISS, suggesting that IGF-1 is a more specific marker of growth in height rather than body weight or composition. Growth hormone deficiency (GHD) in children is associated with higher body mass index (BMI) compared to those with idiopathic short stature (ISS) due to several factors. These include the lack of growth hormone's lipolytic activity, which normally promotes fat breakdown, leading to increased fat accumulation in GHD children. Additionally, parents of children with short stature may overfeed them in an effort to promote growth, and GHD children often exhibit decreased physical activity, further contributing to higher BMI.

These findings underscore the importance of considering multiple factors, including anthropometric measures and hormone levels, when evaluating and managing children with growth disorders. This relation is summarised in many studies and compared to the present study in Table 5.

Conclusion

In conclusion, the present study aligns with existing literature, showing that sex steroid priming significantly increases IGF-1 levels, especially in GHD children compared to ISS, supporting its diagnostic utility in revealing the somatotrophic axis's capacity. However, the lack of significant differences in peak GH levels between primed and non-primed groups suggests that while IGF-1 response is enhanced, peak GH levels during stimulation tests may not be as reliable in predicting IGF-1 dynamics. These results advocate for the use of sex steroid priming in the differential diagnosis of GHD and ISS, while emphasising the need to consider both IGF-1 levels (pre- and post-priming) and anthropometric measurements in

assessing growth potential.

Table 5: Summary of Findings Across Various Studies

Author	Year	Number of Patients	Findings after Sex Steroid Priming
Current Study	2024	63	Significant increase in IGF-1 levels in the primed group; No significant difference in peak GH levels between primed and non-primed groups.
Leger et al.	2021	85	IGF-1 levels significantly increased in prepubertal children after oestrogen priming; Improvement in diagnostic sensitivity for GH stimulation tests.
Clayton et al.	2020	67	Testosterone priming significantly increased both GH and IGF-1 levels; Reduced variability in IGF-1 response.
Massa et al.	2019	55	Modest increases in IGF-1 levels after sex steroid priming, particularly in children with ISS; Timing and dosage affect variability in response.
Mauras et al.	2018	72	Both oestrogen and testosterone priming increased IGF-1 levels; Testosterone had a more pronounced effect.
Binder et al.	2017	40	Sex steroid priming increased IGF-1 levels; No significant change in peak GH levels during stimulation tests.
Bang et al.	2016	60	Variable correlation between IGF-1 levels and peak GH response; Some children with low peak GH still showed substantial IGF-1 increase.
Mullis et al.	2015	50	Oestrogen priming increased IGF-1 levels but did not consistently correlate with peak GH levels in girls with Turner syndrome.
Cohen et al.	2014	100	Enhanced IGF-1 responses with sex steroid priming; Peak GH levels did not consistently predict GHD severity or distinguish it from ISS.

Strong Points of the Study:

- The study performed a clear comparison between primed and non-primed groups, with comprehensive analysis using multiple measurements (IGF-1SD, peak GH levels, and anthropometric parameters).
- The findings are consistent with existing literature, validating the results and contributing to paediatric endocrinology research.

Weak Points of the Study:

- The sample size may be insufficient to detect subtle differences or account for variability within subgroups.
- The study focuses on short-term outcomes, lacking assessment of long-term growth and potential side effects.
- Correlation analysis could be enhanced by exploring additional confounding factors, such as genetic influences.

Future Research

Further research is needed to provide a more comprehensive understanding of sex steroid priming in growth management, particularly in examining long-term growth outcomes, side effects, and the impact of genetic factors in influencing IGF-1 response.

Citation: Nada Alaaraj, Ashraf Soliman, Ahmed Elawwa, Fawziya Alyafei, Noor Hamed, Shayma Ahmed, Ahmed Aqel, Mohamed Qusad, Hendeh Zirak, Nagwa Eldarsy, Sohair Elsiddig, Zeyad Elawwa, Adv Clin Med Sci, "Assessing IGF-1 Response to Sex Steroid Priming in GH Stimulation: Differentiating Growth Hormone Deficiency from Idiopathic Short Stature". 2024; 2(2): 111

Received Date: October 24, 2024; Published Date: October 31, 2024