

The Effect of Growth Hormone on Thyroid Function during Treatment Children with Short Stature

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Abstract: ***Objectives:** to evaluate the effect of GH therapy on thyroid function and the frequency of hypothyroidism during GH therapy. **Patients and methods:** This is retrospective observational study of 120 children (62 male and 58 female) treated with rGH at Endocrine clinic in Benghazi children hospital (2002 - 2017), Study variables of all cases were evaluated as follows: age, sex, indication of GH, age at starting therapy, duration of treatment, height at initiation of GH therapy, height velocity in 1st year of therapy, height velocity in 2nd year of therapy. **Results:** This study shows that shifts in thyroid hormone levels are common during the first year of GH therapy in children who are initially euthyroid. **Conclusion:** GHD is the most common indication of GH therapy. All indications showed significant 1-year treatment response to therapy. Younger age at initiation of rGH therapy was independently associated with significant response to therapy suggesting the importance of identifying children with short stature and prompt initiation of GH therapy. Shifts in thyroid hormone levels are common during the first year of GH therapy in children who are initially euthyroid and post GH hypothyroidism is uncommon.*

Keywords: growth hormone, short stature, hypothyroidism

1. Introduction

Growth hormone (GH) is a necessary factor for normal constitutional and pubertal growth in children. (1)

Growth hormone (GH) is a 191 amino-acid single chain polypeptide, which is secreted by the somatotrophs in the anterior pituitary. (2-3)

Secretion of GH in pulsatile fashion under the regulation of hypothalamic hormones. where the secretion of growth hormone releasing hormone (GHRH) stimulates GH release and somatostatin inhibits GH release, accounts for the rhythmic secretion of growth hormone. (3)

Also, Ghrelin, a peptide hormone produced in the arcuate nucleus of hypothalamus and in much greater quantities by the stomach stimulate secretion of GH. (4)

Physiologic factors also have a role in the stimulation and inhibition of GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH, whereas hyperglycemia, hypothyroidism, and glucocorticoids inhibit GH release. (5)

Recombinant GH was first approved by the United States Food and Drug Administration (FDA) for children with growth failure due to GH deficiency (GHD). Since then, GH has been approved for children with short stature or growth failure in other disorders that are generally not associated with deficiency of endogenous GH production. (6-7)

Patients should be evaluated every 3-6 months, Increases in height and height velocity are the most important markers of response to GH treatment. Monitoring of serum IGF-1 levels is recommended for assurance of compliance, dosing, and safety considerations. Hypothyroidism may occur during the

GH treatment; hence, thyroid function assessment should be considered periodically. (8-9)

Side effects of GH:

- 1) Treatment with rhGH is assumed to induce insulin resistance. This GH effect is observable, as type 2 diabetes mellitus, The incidence and age at diagnosis of type 1 diabetes mellitus during rhGH treatment is similar to the general population. (10)
- 2) Post GH therapy hypothyroidism
- 3) Prepubertal gynecomastia is a rare and self-limited adverse effect, there is no need for alteration in rhGH dosage, or discontinuation of medication. (11)
- 4) Slipped capital femoral epiphysis (SCFE) is defined as a posterior and inferior displacement of the proximal femoral epiphysis on the femoral neck. It occurs more frequently in periods of rapid height gain. Children with GHD are more prone to the development of SCFE, and rhGH replacement therapy may increase that risk by sevenfold.
- 5) (12)
- 6) Benign intracranial hypertension (BIH) or pseudotumor cerebri is the result of the physiological antidiuretic effect of rhGH. If the diagnosis of pseudotumor cerebri is confirmed, rhGH should be discontinued temporarily, and reinitiated later on, at lower doses. (13)
- 7) Significantly increased rate of leukemia in children treated with rGH therapy compared with the age, race, and gender matched general population. (14)
- 8) Transient fever and allergic reaction, including swelling, rash and pain at the injection site.

Post GH therapy hypothyroidism:

Several mechanisms have been proposed to explain the interaction between GH and thyroid function. (15)

- 1) Increased peripheral deiodination of T4 to T3, this hypothesis supported by most studies. (16)
- 2) Decreased binding capacity of thyroxine binding globulin

and other serum binding proteins after high dose GH therapy, most studies suggest that the alterations in thyroid status with GH therapy are unlikely to be significantly influenced by alterations in binding proteins. (16-17)

2. Literature Survey

A retrospective analysis done to study efficacy and safety of GH treatment in children with short stature in Italy 1999 - 2012, on 711 children (59% male and 41% female) and most common indication was GHD then Turner syndrome, the median age at starting treatment for all indication 9.6 years, median duration of treatment 2.6 years with median growth velocity for all indications 4.6cm in first year. (18)

Study in USA done on 5757 children (68% male and 32% female) and most common indication was GHD, ISS then turner syndrome, the median age at starting treatment 10.8years with duration 2years, Patients in all treatment groups had positive changes in Ht SDS over 1st year ranged from 0.4 for ISS to 0.7 for GHD. (19)

A retrospective cohort study done in Taiwan to identify factors influencing the effect of GH therapy on ethnic Chinese children with GHD. 51 patients (13 girls and 38 boys) age at time starting treatment (11.37 ± 1.81), the height velocity for first-year GH therapy was 7.61 ± 1.46 . (20)

Cross-sectional retrospective study done on children treated with GH in a major hospital in Kuwait between December 2013 and December 2014, Sixty patients were treated with GH during the study period of whom 31 (51.7 %) were males. With median age at initiation was 9.0 (6.2-10.7) years, The most common indications for GH therapy were Growth Hormone Deficiency (GHD) 23 (38.3 %), Idiopathic Short Stature (ISS) 12 (20.0 %) and Small for Gestational Age (SGA) 9 (15.0 %). All indications except for ISS showed significant 1-year treatment response to therapy. (21)

A total of 6928 children with idiopathic isolated GH deficiency (n = 5162), neurosecretory dysfunction (n = 534), idiopathic short stature (n = 871), or born short for gestational age (n= 335) who started treatment between 1985 and 1996 participated in the study. Follow-up data on vital status were available in September 2009 done on children treated with GH in France, (65% male and 35% female), With median age at initiation was 11 years, The most common indications for rGH therapy GHD then ISS. (22)

Study done on 2011 in Egypt about growth response of Egyptian children with idiopathic short stature during four years of growth hormone therapy on 120 cases, 90 males (75%), with a mean age of 13.8 ± 2.7 years and 30 females (25%), with a mean age of 12.3 ± 2.5 years, patients showed catch up growth during 1st and 2nd years were the mean height SDS gains during 1st and 2nd years was 0.5 ± 0.5 and 0.4 ± 0.4 respectively. (23)

Aim of the study:

The study done to review of children treated with GH therapy at Endocrine clinic in Benghazi children hospital (2002 - 2017):

- 1) Describe the pattern of use GH therapy.
- 2) Assessment the effect of GH therapy on growth and final height in children with short stature.
- 3) Evaluation of the effects of GH replacement therapy on thyroid function in this group.
- 4) The frequency of post GH therapy hypothyroidism.

Patient and method:

We retrospectively reviewed the medical records of 120 children (62 male and 58 female) with short stature who were diagnosed and treated with rGH between January 2002 till January 2017, in our center (Endocrine clinic in Benghazi children hospital). Children with organic brain lesions, systemic diseases, or syndromes that result in growth disorders (apart from Turner syndrome) were excluded.

They were categorized according to indication of therapy to four groups namely: Growth Hormone Deficiency (GHD), idiopathic short stature (ISS), Small for Gestational Age (SGA) and Turner Syndrome (TS).

The diagnosis of growth hormone deficiency (GHD) in children with short stature is based on clinical features and on one or two stimulation tests were subjects underwent GH provocation tests with insulin and L-dopa.

ISS was defined by a height below - 2 SDS without any findings of underlying disease as evident by a complete evaluation by a pediatric endocrinologist including stimulated GH levels.

Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for the gestational age, compared to a gender. Turner syndrome diagnosed by chromosomal study (karyotyping).

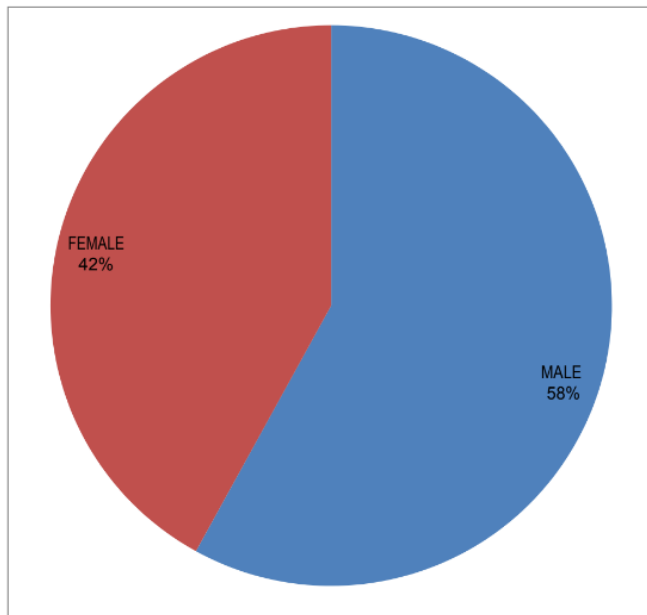
The medical records of identified patients were reviewed and data were extracted. The data included baseline information before and during rGH therapy such as: date of birth, age at initiation of rGH therapy, gender, duration of treatment, anthropometric measures (weight, height, and body mass index [BMI]), height at initiation of GH therapy, height velocity in 1st year of therapy, height velocity in 2nd year of therapy. Magnetic Resonance Imaging (MRI) of the brain done for all children and patients with organic brain lesions were excluded. All children included in the study had normal CBC, blood sugar, renal and hepatic functions. Thyroid function including T4, T3 and TSH collected before and after one year from initiation of rGH. All children are euthyroid before therapy, thyroid function T3, T4, TSH within normal range except for 2 patient T4 were near the lower end of the normal range.

3. Results

This study is a retrospective case series observational study of 120 children with short stature who were diagnosed and treated with rGH between January 2002 till January 2017

120 children near half of them are Growth hormone deficiency (GHD), (n= 48; 40%) then idiopathic short stature (ISS), (n=36; 30%), small for gestational age (SGA), (n=22; 18.4%) and Turner syndrome (TS), (n=14; 11.6%). See

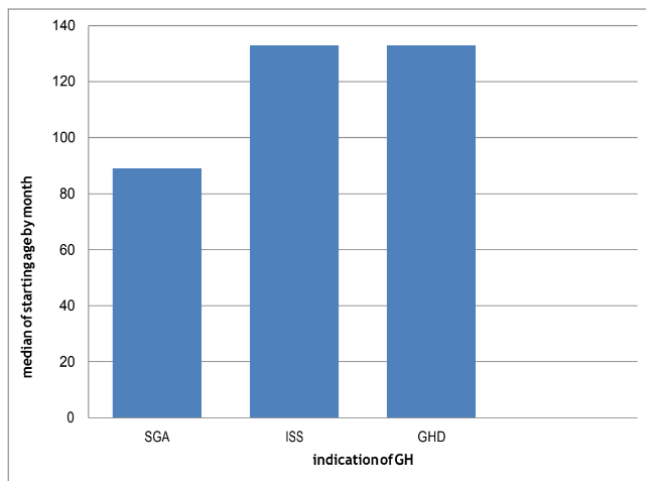
figure (1)

**Figure 1:** Gender distribution of study population**Age at starting treatment:**

Age of starting treatment was not normally distributed (Shapiro Wilk test $P < 0.001$). It ranged from 18mo (1.5years) to 216mo (18years) with median age of 133 months (11years)

Age at starting treatment according to diagnosis:

Median age at starting treatment was similar in GHD and ISS categories 11yr (133mo) while much younger in SGA category 7yr/5mo (89mo). See figure (3) The difference was statistically significant.

**Figure 2:** Treatment Starting age in months across major etiological categories.

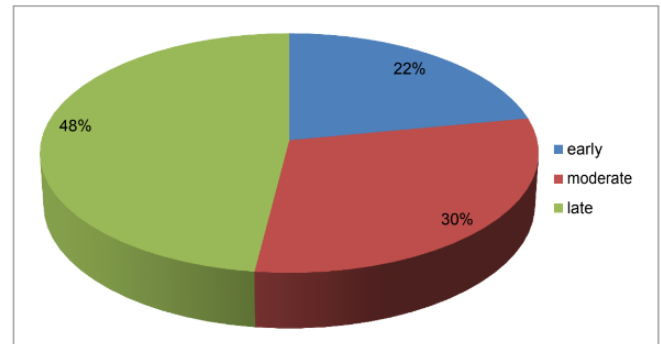
Kruskal Wallis $P = 0.012$

Mann-Whitney $P = 0.002$ (ISS x SGA)

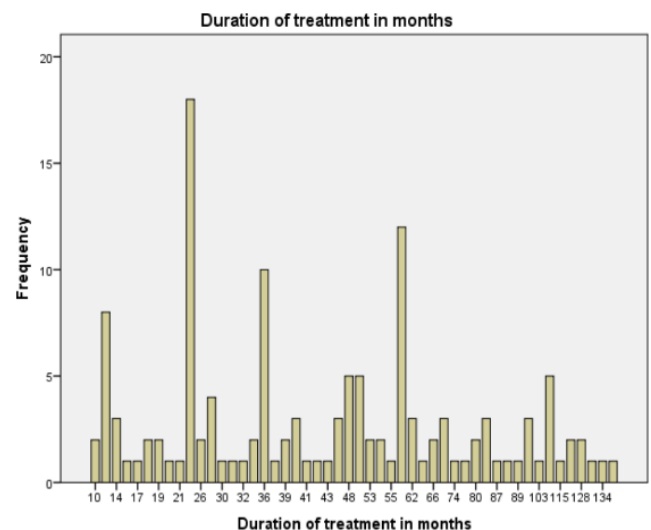
Treatment related factors:**Age group of starting therapy:**

Near half of cases started treatment at later time. Only less than quarter of cases started treatment early. See figure (4)

Early < 8yrs / Moderate 8 - 11yrs / Late > 11yrs

**Figure 3:** Distribution of patients according to age group of starting treatment.**Duration of treatment:**

Duration was not normally distributed (Shapiro Wilk $P < 0.001$). Duration of treatment ranged from 10 months to 145 months (12 years) with median of 41 months (3.5years). See figure (5)

**Figure 4:** Duration of treatment frequency bar chart**Duration of treatment according to diagnosis:**

Median duration of treatment for ISS category was 3yr (36mo) which was the lowest. The highest treatment duration was among GHD category 5yr (60mo) while among SGA the median duration of treatment was 3.7yr (43 mo). See figure (6)

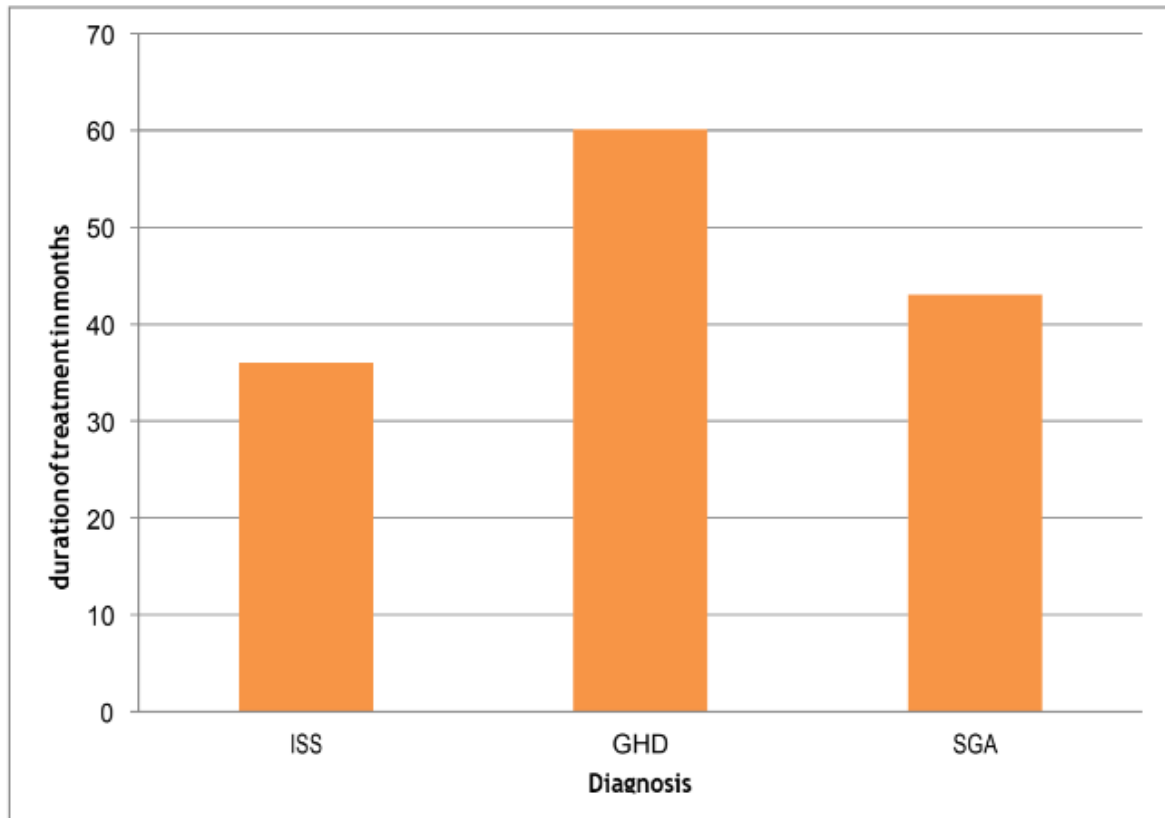


Figure 5: Duration of treatment in months across main etiological categories.

Kruskal Wallis $P = 0.001$

Mann-Whitney $P < 0.001$ (ISS x GHD)

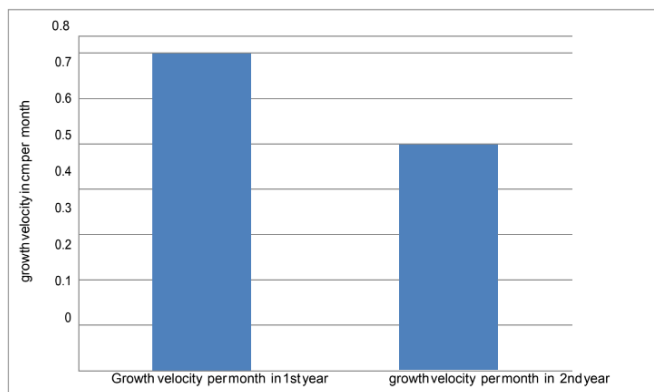


Figure 6: Growth velocity comparison between two years of treatment per month.

$P < 0.001$ by Wilcoxon signed rank test

Growth outcomes:

Stature growth velocity per month across two years of treatment in total study population:

Growth velocity was normally distributed during the first year of treatment (Kolmogorov-Smirnov $P = 0.2$), with mean = 8.28 cm per year (0.69 cm per month). During second year the growth velocity was not normally distributed (Kolmogorov-Smirnov $P < 0.001$), with median of 6 cm per year (0.5 cm per month). The difference of median growth velocity between first and second year was significant. See figure (7)

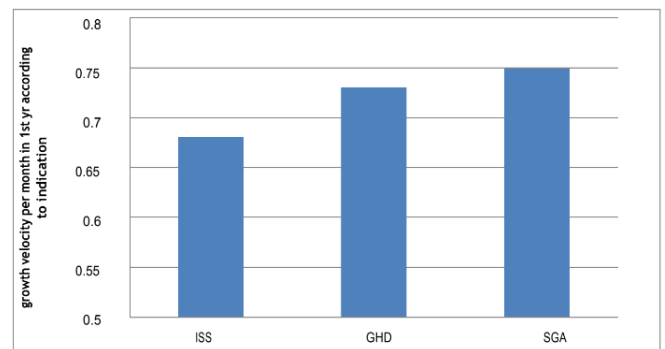


Figure 7: Growth velocity during the first year of treatment across main three diagnosis categories

Kruskal Wallis $P = 0.674$

Stature growth velocity per month across two years of treatment according to diagnosis:

Median stature growth velocities during first year for ISS, GHD and SGA are 8.16, 8.76, and 9 cm/yr (0.68, 0.73 and 0.75 cm/month) respectively see figure (5.8) and during the second year were 6, 6.9 and 6 cm/yr (0.5, 0.58 and 0.5 cm/month) respectively. see figure (5.9). No significant difference in growth velocities across the three categories in either years of treatment.

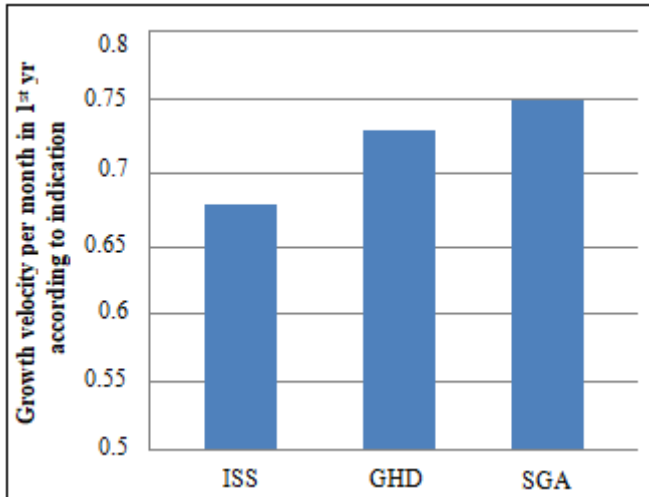


Figure 8: Growth velocity during the second year of treatment across main three diagnosis categories
Kruskal Wallis $P = 0.466$

Stature growth rate differ significantly in all categories across the two years. See figure (10) for ISS, figure (11) for GHD and figure (12) for SGA categories.

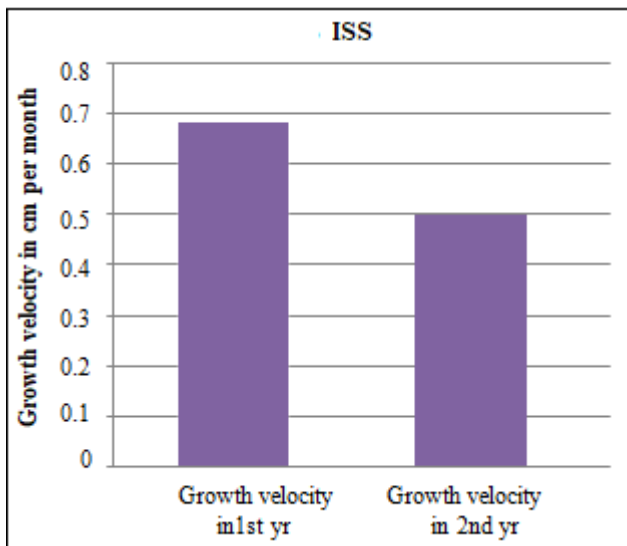


Figure 9: Growth velocity in ISS category across the two year of treatment Wilcoxon signed

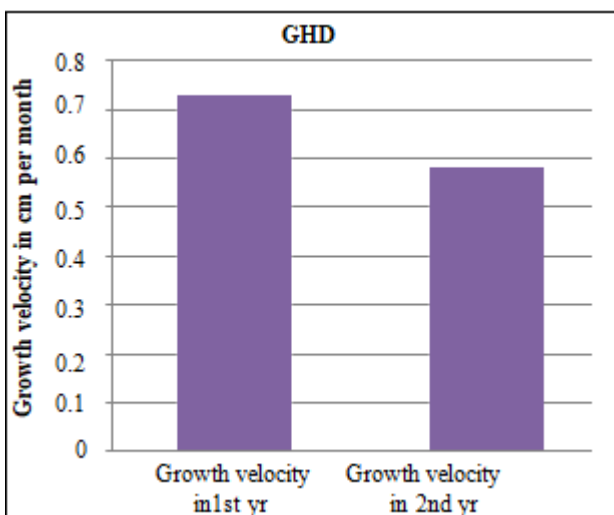


Figure 10: Growth velocity in GHD category across the two

year of treatment Wilcoxon signed rank test results $P = 0.001$

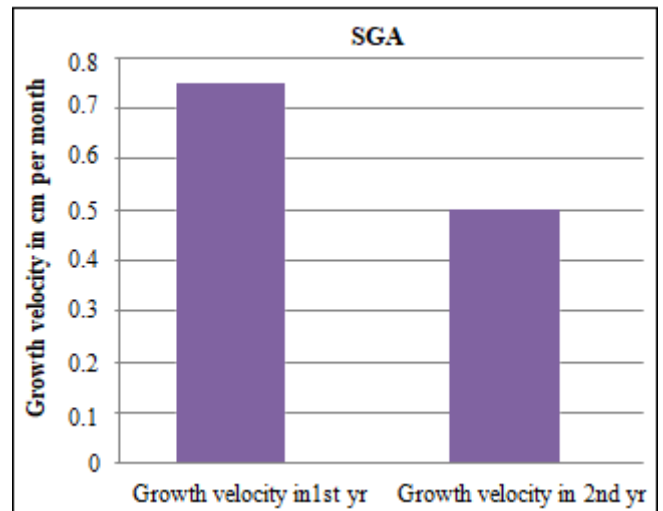


Figure 11: Growth velocity in SGA category across the two year of treatment Wilcoxon signed rank test results $P = 0.001$

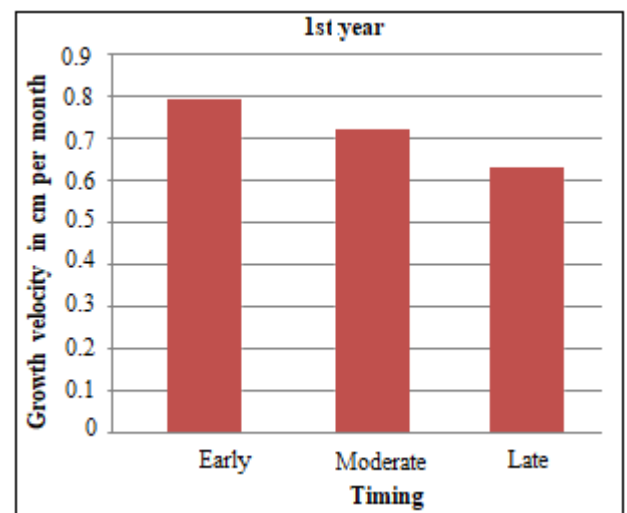


Figure 12: Stature growth velocity per month during first year according to starting age of therapy

Kruskal Wallis $P = 0.029$, ANOVA $P = 0.015$ Bonferroni P (early versus late treatment) = 0.018

The stature growth velocity in first year for all cases early, intermediate and later treatment was normally distributed (Shapiro Wilk $P = 0.892, 0.365, 0.892$ respectively) and mean values were 9.5, 8.6, 7.5 cm per year (0.79, 0.72 and 0.63 cm per month) respectively. Difference was significant for early versus late treatment start sub cohort comparison. See figure (13)

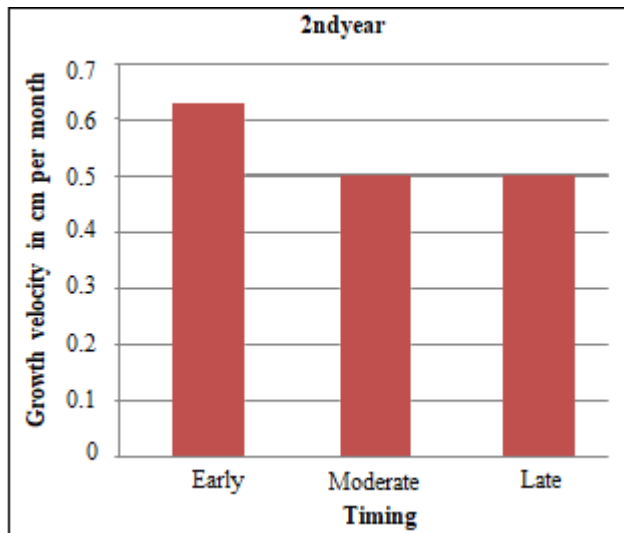


Figure 13: Stature growth velocity per month during second year according to starting age

Kruskal Wallis $P = 0.188$, ANOVA $P = 0.487$

The stature growth velocity in second year was normally distributed for intermediate treatment start sub cohort and not in early and late ones (Shapiro Wilk $P = 0.8$, 0.021 , 0.01 respectively) and median values were 7.5 , 6 , 6 cm per year (0.625 , 0.5 and 0.5 cm per month) respectively. See figure (5.14)

Alterations in thyroid function:

No significant change in mean serum TSH after rGH therapy from 2.26 to 2.43 mIU/L, mean serum T3 level non significantly increased from 2.58 to 2.77 pmol/L and significantly decrease in mean level of T4 from 121 to 107 nmol/L. Table (.1)

Table 1: Alterations in TFT after GH therapy

TFT	Before Therapy	One year after therapy	Normal range
TSH	2.49mu/L	2.56mu/L	0.5 - 5mu/L
T3	2.57nmol/L	2.58nmol/L	1.3-3.1nmol/L
T4	117.1nmol/L	103.9nmol/L	65-160nmol/L

According to Paired Sample Test for TSH $t = 0.362$ and $P = 0.719$

For T3 $t = 0.031$ and $P = 0.975$ for T4, $t = 3.119$ and $P = 0.003$

Table 2: Diagnosis and post GH hypothyroidism

Diagnosis	Post GH hypothyroidism		Total
	Yes	No	
GHD	2	46	48
	4.2 %	95.8%	100.0%
ISS	0	36	36
	0.0%	100%	100.0%
SGA	0	22	22
	0%	100%	100.0%
Total	2	104	106
	1.9%	98.1%	100.0%

4. Discussion

This study aimed to describe the pattern of use of rGH, the treatment outcomes and its effect on thyroid function. The study revealed that the most common indication for the use of rGH among children with short stature is GHD. which is similar to other reports in literature where study done in Italy on 711 children, most common indication was GHD then Turner syndrome. (18), Study in USA, most common indication was GHD, ISS then turner syndrome (19). Cross-sectional retrospective study done on children treated with GH in a major hospital in Kuwait, the most common indications for GH therapy were growth hormone deficiency (GHD), Idiopathic Short Stature (ISS) and then Small for Gestational Age (SGA). (21) Study done in France most common indication is GHD. (22)

120 children were treated with rGH during (2002-2017) of whom 62 (58%) were male and female 44 (42%), after excluding children with Turner syndrome, this means there is difference was found in gender of those who received rGH therapy, which is similar to other reports described in the literature, were study done on Italy children treated with rGH 59% of whom male and 41% female (18), study in France 65% male (22), A retrospective cohort study done in Taiwan to identify factors influencing the effect of GH therapy on ethnic Chinese children with GHD 51 patients (38 boys and 13 girls) (20). Study done in Kuwait, sixty patients were treated with GH during the study period of whom 31 (51.7 %) were males (21), in Egypt study done on children with ISS was 75% male (27) and in USA study 68% male (19).

Age of starting treatment on our study ranged from 18months (1.5years) to 216months (18years) with median age of 133 months (11years) for all indications, which is similar to other reports described in the literature, in France study median age (11 years) (22), 10.8 years in USA study (19), 11 years in study from Egypt (23) and earlier age in Kuwait, Taiwan and Italy, were median age of children in Kuwait study was 9 years (21), in Taiwan study 9.5years (20) and in Italy study 9.6years at time of starting rGH therapy. (18)

Duration of treatment for children in this study ranged from 10 months to 145 months (12 years), with median of 3.5 years. median duration of treatment for ISS category was 3 years which was the lowest. The highest treatment duration was among GHD category 5 years, while among SGA the median duration of treatment was 3.6 years. Duration of rGH therapy in reports described in the literature deferent and depended on indication, in Italy study median of duration in all indications was 2.6 years (18) and in USA study was 2years. (19)

In our study after period of follow up, growth velocity during the first year of treatment with mean = 0.69 cm per month (8.28 cm/yr), and during second year the growth velocity with median of 0.5 cm per month (6 cm/yr), as reports described in literature the difference of growth velocity between first and second year was significant. (18-23)

Median stature growth velocities during first year for ISS, GHD and SGA are 8.16 , 8.76 and 9 cm respectively, this

means the best response to rGH therapy in stature velocity in first year was SGA children similar to study done in USA were the best response to treatment was SGA (19) and in study done in Kuwait GHD is the best response for rGH therapy in first year. (21)

In the present analysis, it was found as reported in the literature that younger age at initiation of therapy is significantly associated with good response to the treatment in all indications combined. Shifts in thyroid hormone levels are very common during the first year of GH therapy in children who are initially euthyroid, this theory has been proven by most of the studies that were conducted to see the effect of growth hormone therapy on thyroid function. Our study like other studies mentioned in literature (24-27) where we found a significant decrease of T₄ serum concentration in most children with no significant changes in T₃ and TSH levels. Hypothyroidism as a result of treatment with growth hormone is uncommon in our study, approximately 1.9% among all children who received growth hormone therapy, and compared to the research mentioned in the literature, it is considered a small percentage, where In 2010 retrospective study done by Joanna et al. (24) on 75 children treated with GH, During initial 3-6 months of rGH administration, a significant decrease of T₄serum concentration in most children and in 17 children (22%), hypothyroidism was diagnosed and L-T₄substitution was administered. (24) and in 2007, study done by Agha et al. retrospective review of 243 patients with severe GH deficiency, before GH treatment, 159 patients had treated central hypothyroidism (treated group) while 84 patients were considered euthyroid (untreated group). In the untreated group observed a significant reduction in serum T₄ concentration without a significant increase in serum T₃ or TSH concentration, 30/84 patients (36%) became hypothyroid and needed initiation of T₄ therapy. (25)

It is possible that the GH deficiency seen in the majority of patients with pituitary/hypothalamic disorders may mask hypothyroidism in some patients by giving a relatively high serum T₄. GH therapy may then unmask the hypothyroidism (24-27). In accordance with such a mechanism GH deficient children evaluated thoroughly to exclude secondary thyroid failure before GH administration do not develop thyroid insufficiency during GH substitution therapy. It is suggested that thyroid insufficiency should be considered in GH deficient patients with low normal serum T₄ (27).

Our study has several limitations including small number of patients and short period of follow up. Because of this we were unable to detect meaningful differences and difficult to evaluate safety of long term therapy with rGH. The study was a retrospective review which relied on obtaining data from medical records, there was no data on some parameters. Despite this, it was an observational study of a real life use of rGH.

5. Conclusion

The study revealed that the most common indication for the use of rGH among children with short stature is GHD. There is gender deference in receiving rGH where GH indicated in male more than female, duration of therapy is variable

according to indication, younger age at initiation of rGH therapy was associated with significant response to the treatment at 1-year follow-up. The difference of growth velocity between first and second year was significant. In our study there is significant transient decrease in T₄ within normal range and non significant changes in T₃ and TSH in previously euthyroid children during the first year of GH therapy in most of patients. Only two euthyroid children developed central hypothyroidism during rhGH were diagnosed as GHD before treatment and their T₄ level was near the lower end of the normal reference range.

6. Future Scope

Our study indicate that final height is increased with early therapy, thus the earlier the diagnosis, the better the prognosis for height. So it is important that primary care providers give early referral to an endocrinologists for evaluation of children with short stature and those with low growth velocity. Our study has some limitations. Firstly, diagnosing central hypothyroidism is not easy. Although a (very) low FT₄ in combination with a normal TSH concentration in the absence of non thyroidal illness is strongly suggestive of this condition, FT₄ concentrations around the lower limit of the reference interval are often difficult to interpret

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