The Child and Newborn

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Editorial

Sorry……..

This issue goes to your hands after a long delay. I am sorry for the delay . Personal matters as well as non availability of articles has been the reasons. A request goes to all members especially executive board members to atleast give one article per year to sustain a regular publication of this journal.

Pediatric endocrinology is an important subject as well as handicapped one due to lack of experts in this field in our country. A casual look at the membership of Indian society for Pediatric and Adolescent Endocrinology revealed a membership of around 150 with less than 5 members from West Bengal.

A universal screening of newborns for hypothyroidism is still a dream in newborns delivered at most of places except for some corporate hospitals. A thyroid hormone testing and as for that matter any investigation for endocrine diseases except for blood sugar is inhibitory for the general population. Added to it is that these investigations need to be repeated frequently atleast in the beginning. As we are proceeding for attaining MDG goals a lot of work needs to be done in easing out these hurdles in proper management of these cases.

The investigations performed at different laboratories vary sometimes. It is more so important as regards to endocrine diseases because most of the therapies are meant for the whole life and being costly a second opinion becomes monetarily difficult. Its true that some labs do not maintain standards but its also true that there are some factors which may alter results if some precautions are not properly adhered to. The first and foremost rule that should be adhered to is that the investigation is going to supplement my proper clinical evaluation. The child should be properly prepared ie fasting if required, interfering medications or food stuff barred and clinically able to take up tests requiring stimulation or suppression. Proper calculation of drugs should be done prior to beginning by taking aproper height and weight.A proper venous access is important because many tests need to be conducted at fixed intervals and a improperly done venous access may ditch us at times. Proper labeling and early transport are two most important factors determining accuracy of results.

There are certain endocrine conditions which are not properly correctible and the person has to live with that disability in this cruel society. They have to be psychologically rehabilitated . Proper counseling is sometimes required and proper trained and understanding counsellars are in very much shortage.

A publication on Clinical Practice guidelines for Type 1 Diabetes Mellitus in Children and adolescents 2011 by Indian society for Pediatric and Adolescent Endocrinology and its availability on net is a good step in this regard to give a standard protocolised management. Similar publications will help the general pediatricians to manage these cases.

As per management newer methods of drug delivery are being tried newer therapies are being planned. On my request Prof Sudip Chatterjee has apprised us of what is going in the International arena. I have put it as editorial to the issue.

Prof. Atul Kumar Gupta
Editor-in-Chief

Editorial

ESPE 2015 Highlights

The meeting of the European Society of Pediatric Endocrinology in 2015 in Barcelona, threw up some interesting nuggets of information, a selection of which is given below.

Glucose monitoring in diabetes: Glucose sensors are evolving rapidly there are models which show real time data on a phone. If sensors are used for less than 80% of the time, there is an association with sub optimal control. Appropriate sensor use is associated with a fall in HbA1c levels in type 1 diabetes. However less than 1/3 of patients agree to wear them most probably due to their loud alarms. A new technology called 'flash monitoring' has been developed. Here a patch is applied over a suitable area of the body and changed every 2 weeks. A reading device when brought near the patch gives a readout of the interstitial fluid glucose. This device called 'Libre', costs around 66 euros but is not yet approved for type 1 diabetes. It is available in India at present at a fraction of the European price.

Endometriosis: Endometriosis has a genetic basis and typically 6 to 12 years pass between the onset of symptoms and laparoscopic diagnosis. Early diagnosis and treatment of endometriosis in teenagers was stressed as the best way to prevent target organ damage. To this end new fine needle endoscopes inserted transvaginally have been usedwith success. This relatively new technology is gaining acceptance.

Energy metabolism: Brown adipose tissue (BAT) received a lot of attention. These fat cells contain numerous fat droplets and many mitochondria and express UCP-1. In contrast white adipose tissue contains one large fat droplet and a single mitochondrion. BAT is metabolically active and is responsible for thermogenesis and weight loss. BAT has been documented by PET scan and MRI angiography and is found in the interscapular, axillary, suprascapular and peri adrenal areas. The amount is relatively more in infants. It was noted many years ago that skin temperature of infants was higher in the interscapular area, a finding now related to BAT. BAT expresses beta 3 adrenergic receptors and efforts are underway to stimulate its proliferation. A drug mirabegron, originally developed to treat hyperactive bladder has been used. Stimulation of BAT if clinically successful, would be an excellent way to combat obesity.

Genetics: New genes have been identified in leptin deficiency, GH excess, hypogonadotrophic hypogonadism, a PraderWili like syndrome, to name a few. The technique of Next Generation Sequencing is a powerful tool that has transformed our understanding of gene mediated disease. Here a condition which may be rare or common is studied. Genes of subjects with the condition are compared to genes of control subjects. The gene sequences that are statistically different between the two groups are found. For example a relatively rare condition like hypogonadotrophic hypogonadism may have 36 gene defects while a condition like inflammation may have over 20,000 genes that are either up or downregulated. To add perspective, the human genome has 3.6 thousand million genes.

Genetics: On the other hand stem cell research did not have much to offer. Pluripotent stem cells can be made from a variety of cells including mature adult cells which can be differentiated into ectodermal, mesodermal and endodermal cells. To be clinically useful, further downstream processing is needed to produce safely functioning mature tissue cells. For example, efforts at developing a safely functioning beta cell from say pancreatic duct cells, are yet to bear fruit.

Reproductive medicine in childhood cancer: Technological advances in reproductive medicine have spilled over to pediatrics. It is now theoretically possible to preserve child bearing potential in female cancer patients irrespective of age, but not in leukemias (because of cell rests in the ovary). Depending on the type of cancer ovarian, or oocyte cryopreservation can be offered. Cryopreserved ovaries from a donor has been used in Turner (TS) patients resulting in pregnancy. Americanregulations are more stringent than European ones in limiting access to ART for Turner patients (due to the risk of aortic dissection). While GH is now accepted treatment in TS, the timing of estrogen replacement has been a matter of controversy. Latest data suggest that very early initiation of ethinyl estradiol at 25ng/kg/day to girls as young as 7 years together with GH produce the best final height. Treatment needs close monitoring to prevent early onset of pubertal changes.Klinefelter Syndrome (KS) patients have some possibility of parenthood with preservation of sperm and or sperm precursor cells once the age of 18 years is reached.

Neonatal diabetes received a fair share of importance. The seminal work of Professor Hattersley was again on display. In fact his group does genetic analysis free of charge on any patient whose samples are sent to him.

Overall, the conference gave an excellent overview of the state of pediatric endocrinology today. The overarching feature was that next generation sequencing has brought about a paradigm shift in the way we look at many endocrinological conditions.

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Case Report

Forme Fruste Choledochal Cyst and Acute Abdomen in A Child

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Abstract:

We report a case of a 10 year old female child with acute pain abdomen, vomiting, conjugated hyperbilirubinemia with raised serum lipase and amylase levels, diagnosed as forme fruste choledochal cyst which is a variant of choledochal cyst associated with pancreatico biliary malunion.

Key words: choledochal cyst, forme fruste choledochal cyst, pancreatico-biliary malunion

Introduction:

Choledochal cysts are defined as cystic dilatations of the extrahepatic and/or intrahepatic biliary tree. They are rare in Western populations - but are more commonly seen in Eastern countries. They affect female more often than male. Although frequently present since infancy or childhood, as many as one half of the patients would have reached adulthood at the time of diagnosis. Classic clinical triad of abdominal pain, jaundice, and a mass is less commonly seen[1]. Symptoms vary according to age at presentation. Obstructive jaundice is mainly seen in children, whilst abdominal pain is the commonest feature in adults. Acute symptoms suggest the presence of complications such as cholangitis, pancreatitis or perforation[2].

Forme fruste choledochal cyst (FFCC) is known as a variant of a choledochal cyst that has minimal or no dilatation of the extrahepatic bile duct (EHBD) and is associated with pancreatico-biliary malunion (PBMU)[3].

Case report:

A 10 year old female child presented with a history of jaundice 7 days and pain abdomen 2 days. Pain was acute in onset, diffuse, continuous and radiating to back, associated with vomiting. Jaundice was progressive, with clay colored stool, pruritus, and dark urine. There was no history of fever, anorexia, burning micturition, drug intake, bleeding manifestation or altered sensorium.

There was past history of hospitalization for similar episode of pain abdomen 3 months back, when the child was diagnosed to have acute pancreatitis and was treated conservatively. No history of contact with T.B. or of blood transfusion. No history of similar illness in any family member. She was completely immunized for her age.

On admission her higher mental functions and vitals were normal. There was icterus and the abdominal examination revealed diffuse tenderness with guarding. Overlying skin was normal, and there was no organomegaly or ascites.

Complete blood counts and renal function tests were within normal limits. LFT was deranged with raised serum level of SGPT, ALP and conjugated bilirubin. Serum amylase and lipase levels were also elevated. Chest x ray was normal. Serology for HIV 1 and 2, HBsAg, anti-HCV , anti HAV and Mantoux test were negative. USG whole abdomen showed distended gall bladder, dilated CBD and MPD. MRCP showed dilated biliary tree with choledocholithiasis , distended gall bladder with sludge in lumen and mildly dilated MPD. She underwent endoscopic sphincterectomy with stone extraction and CBD stenting. Stent was removed after 6 weeks.

She was followed up for 3 months and a repeat MRCP (Fig 1 below) showed CBD diameter of 6 mm and configuration of biliary tract suggestive of "forme fruste choledochal cyst": disproportionately central dilation (white arrow) extending till left hepatic duct, grossly distended gall bladder and a long common channel(black arrow). Currently she is waiting for her surgery in the form of EHBD excision and hepaticojejunostomy.

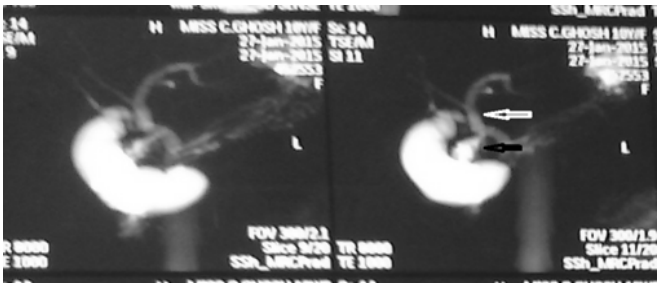

Fig 1 Showing Forme Fruste Choledochal Cyst

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Discussion :

Cystic dilation of the biliary ducts, also known as a choledochal cyst, is a rare but serious condition that requires treatment in the form of surgery. Although these are frequently present from infancy / childhood, the disease is more commonly diagnosed in adults. The incidence of choledochal cysts is only between 1 in 100,000 to 1 in 150,000 people in Western countries but is much more common in Eastern countries such as Japan. They occur three to eight times more commonly in women. This congenital disorder involves isolated or combined dilatation of the extrahepatic or intrahepatic biliary tree[4].

Todani modified Alonso-Lej classification of Choledochal Cyst is as follows[4] :

Type I: Dilatation of the extrahepatic biliary tree

Type II: Diverticular dilatation of the extrahepatic biliary tree

Type III: Cystic dilatation of the intraduodenal portion of the common bile duct (choledochocele)

Type IVa: Dilatation of the extrahepatic and intrahepatic biliary tree

Type IVb: Dilatation of multiple sections of the extrahepatic bile ducts

Type V: Dilatation confined to the intrahepatic bile ducts (Caroli's disease)

Lilly *et al* in 1985 described four patients having stenosis of the distal common bile duct, a 'long common channel' beyond proximal junction of the common bile and pancreatic ducts, cholecystitis and the classical pathological microscopic features of choledochal cyst in the wall of the common bile duct and coined the term "forme fruste choledochal cyst" (FFCC)[5].

The classic clinical triad associated with choledochal cysts includes right upper quadrant pain, jaundice, and an abdominal mass. Only 10% of patients present with this triad. Adults have a slightly different presentation viz. abdominal pain and jaundice; in contrast, children because of a higher incidence of bile calculi or sludge and pancreatico-biliary ductal malformation (FFCC) can present as acute pancreatitis, cholangitis, and/or cholelithiasis[6]. FFCC represents 4-21% of all choledochal cysts. The presenting symptoms include recurrent abdominal pain, recurrent jaundice, fever and pancreatitis which closely resemble those seen in patients with classical choledochal cyst[7]. The differentiation of FFCC from choledochal cyst is essentially done on findings of contrast enhanced cholangiopancreaticogram (CECP) or intraoperative cholangiopancreaticogram. There is scant literature available on normal dimensions of extra hepatic biliary duct (EHBD) and the common pancreaticobiliary channel in children. The cut off diameter above which the diagnosis of FFCC is unacceptable has been arbitrarily decided as 10 mm previously. The demonstration of a longer common pancreaticobilary channel for a particular age with EHBD measuring less than 10 mm on ERCP or intraoperative cholangiopancreaticogram clinches the diagnosis of FFCC[8]. The available literature mentions the maximum normal diameter of EHBD in children to vary from 3 to 6 mm[9].

The treatment of choice for FFCC in children is EHBD excision and hepaticojejunostomy. Although open sphincteroplasty and endoscopic sphincterotomy have also been reported as treatment modalities for this condition[10], it is not favored because the anatomical abnormality allowing mixing of biliary and pancreatic secretions in the two ductal systems is not fully corrected unless a pancreaticobiliary disconnection is done. Similarly a simple cholecystectomy as prescribed for Pancreatico biliary maljunction in adults is not justified in children[11].

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Common Endocrine Problems in Neonatal Period

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The transition from intra-uterine to extra-uterine life is a unique phenomenon occurring in human body. It is not only the cardiovascular system, but this transition actually affects the entire physiology. As a result frequently endocrine problems are seen during neonatal period, which are often subtle or transient in nature, reflecting the problems of post-natal adaptation. This article is meant to highlight the important endocrine related issues commonly seen during neonatal period and a guide for the treating doctors how to manage them.

Glucose Homeostasis

Hypoglycaemia is a common problem especially in sick or preterm babies.Incidence is variable depending on the definition criteria used in different studies, but according to Cornblath[1] it varies from 5-7% in term newborns and from 3.2 to 14.7% in preterm infants. Respective to weight, it occurs in 8% of Large for Gestational Age (LGA) and up to 15% of Small for Gestational Age (SGA) infants. Based on the World Health Organization (WHO) recommendations (WHO 1997 as cited by Fernández Lorenzo et al 2011) thresholds would be: Sick newborn, (signs of illness) :<2.5mmol/L or 45 mg/dL Healthy term / preterm (feeding well) :< 1.1 mmol/L or < 19.8 mg/dL.

Symptoms of hypoglycemia may range from slight jitteriness to frank convulsions. There are many different causes of hypoglycemia ranging from transient self-resolving process to lifelong debilitating condition. For example, in preterm and IUGR babies, there is low glycogen deposit, restriction in fluids and energy intake, hormonal and enzymatic immaturity etc. leading to transient hypoglycemia. These babies are also prone to hypothermia increasing their energy demand. Usually they recover well with frequent feeding and meticulous monitoring of blood sugar and temperature. Another group of babies show transient hyperinsulinism for example, the infants of diabetic mother, Beckwith-Wiedermann syndrome, Rh-hemolytic diseases. These babies should be monitored frequently, and may require higher GIR (Glucose infusion rate) often through central line placements. Similar situations are also observed in cases of polycythemia, sepsis, perinatal stress. More profound hypoglycemia is noted in case of pancreatic islet cell adenoma, a rare condition requiring very high concentration of glucose. This condition can lead to severe neurological sequel if not managed properly. They usually have very high insulin levels. Long-term management require diazoxide, octreotide, and partial or near total pancreatectomy. Often newborns are noted to have hypoglycemic episodes after they are on full feeds. In this situation inborn errors of carbohydrate metabolism (glucogenosis, hereditary fructose intolerance and galactosemia) or amino-acid metabolism (methyl malonic and glutaric acidemias, leucinosis (MUSD), carnitine deficiency) or defects in fatty acid beta-oxidation etc., should be kept in mind. On suspicion of Inborn Error of Metabolism (IEM), feeds should be stopped and immediate glucose infusions should be started, pending investigation results. Investigation of hypoglycemia includes of taking a critical blood sample during the episode, which includes, blood glucose, serum insulin, C peptide, cortisol, TSH, IGF1 levels, blood gas along with a urine sample looking at ketones.

On the other hand hyperglycemia is rather rare in neonatal period. Neonatal diabetes (incidence 1in 100000) is usually self-resolving within 3 to 6 months' time. However afew reported cases have shown cellular defect leading to permanent diabetes in the child. They typically presents with poor weight gain, polyuria, and diabetic keto acidosis. Although most of them require insulin, some of them do respond to sulfonylurea therapy. IUGR babies often show insulin resistance leading to hyperglycemia, they are often managed with insulin in sliding scale.

Thyroid Disorders

Thyroid dysfunction in the newborn mostly present as hypothyroidism, however cases with thyroid excess are also

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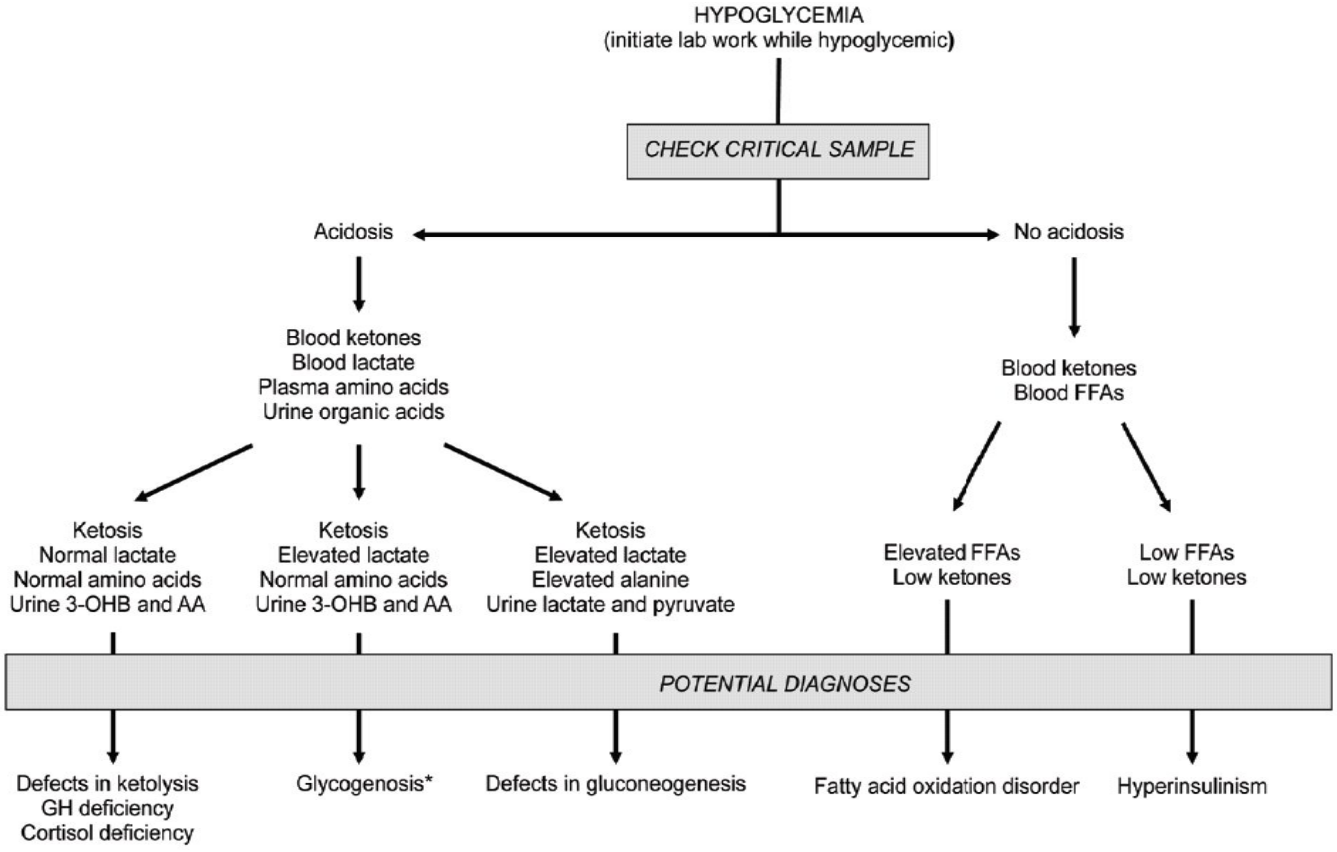

Flow chart showing diagnosis of hypoglycemia - adapted from Fuhrman[3].

not rare. Congenital hypothyroidism in majority are due to agenesis or dysgenesis of thyroid gland itself (85%), and commonly present as ectopic thyroid. Central causes due to pituitary dysfunctions are rare. Transient hypothyroidism can occur due to iodine deficiency, excess maternal anti-thyroid drugs reaching the fetus in utero, or trans-placental passage of maternal thyrotropin receptor-blocking antibodies[4]. Thyroid is crucial for brain development. Clinical signs of hypothyroidism may not be very apparent in newborns. Hence strong suspicion is necessary. Infants may have coarse skin, protruding tongue, constipation, potbellied abdomen and wide open fontanelle. Low thyroxin and elevated TSH levels are key to diagnosis. However, TSH is also a key hormone that helps in neoglucogenesis in neonatal period, hence often remains high and comes back to normal within a few days. In central causes of hypothyroidism TSH may be abnormally low with low thyroxin levels. In recent years, thyroid screening is done in the newborn period to detect hypothyroidism. Following diagnosis supplementation with thyroxin should be initiated at the earliest opportunity.

Hyperthyroidism in the neonatal period is rare, with the most common etiology being maternal Graves' disease, is due to the trans-placental passage of maternal TSH receptor-stimulating antibodies (TSA) to the fetus. Infants usually present as tachycardic, and occasional thyroid enlargements. Usually it is self-limiting and goes away with clearance of maternal antibody from the system. Hence they are managed symptomatically and rarely require anti-thyroid medicine.

Reference range[7]

	T4 (µg/dl) mean (range)	fT4 (pg/ml)mean (SD)/range	TSH (µU/ml)mean (range)
Cord blood	10.8 (6.6-15)	13.8 (3.5)	10.0 (1-20)
1-3 days	16.5 (11-21.5)		5.6 (1-10)
4-7 days		22.3 (3.9)	
1-2 weeks	12.7 (8.2-17.2)		2.3 (0.5-6.5)
2-6 weeks	6.5-16.3	9.0-22.0	1.7-9.1
6 weeks to 12 months	11.1 (5.9-1.3)	13.0-24.0	2.3(0.5-6.5)

Management:

Low T4, TSH>40	Check serum T4, fT4, TSH as soon as possible – if abnormal start treatment
Low T4, TSH < 40	Repeat newborn screen, Check serum T4, fT4, TSH – if abnormal start treatment
Low T4, Normal TSH	Check serum T4, fT4, TSH, consider Transient or central cause, monitor, and treat as necessary
Normal T4,HighTSH	Repeat at 2-4 weeks, Transient or delay in maturation, if normal – no treatment, if persistently TSH>10 – start treatment, and trial off therapy at 3 years of age.
Persistently High TSH (6-10 at 1 month)	Check serum T4, fT4, TSH, if persistently TSH>10 – start treatment, and trial off therapy at 3 years of age.
Low T4 (<3), delayed High TSH	Check serum T4, fT4, TSH at 2 weeks, if persistently TSH>10 – start treatment, and trial off therapy at 3 years of age.

Calcium Homeostasis

Calcium homeostasis is maintained by a complex interaction between calcium intake, mobilization of stored calcium, action of parathyroid hormone, vitamin D and calcitonin. Following interruption of calcium supply from maternal side after birth, there is a drop of calcium level, which stimulates parathyroid, leading to increase in serum calcium. There is a gradual decline in calcium level following this unless there is adequate supply of oral calcium and vitamin D.

Hypocalcemia in the neonate is often defined as a total calcium level < 7.5 mg/dL or an ionized calcium level < 1.20 mmol/L. Hypocalcaemia may be asymptomatic, but may also present as jitteriness, cyanosis, apnea, and seizures. Babies of diabetic mothers, SGA babies, birth asphyxia, and sepsis are more prone to develop hypocalcemia. Laboratory investigations should include serum and ionized calcium, urinary calcium levels, vitamin D and parathyroid hormone levels. Calcium should be supplemented orally in mildly affected cases and intravenously in severe cases. Intravenous supplementation should be slow with cardiac monitoring in place. After normalization of serum calcium oral treatment should follow till adequate calcium intake is ensured, usually taking 3 to 4 weeks.

On the other hand hypercalcemia in newborn period is uncommon, by definition total calcium level should be > 10.5 mg/dl. However symptoms are not usually seen till total calcium is > 12 mg/dl and ionized fraction is >1.5 mmol/L[5]. Infants present with excessive irritability, seizures. Rarely subcutaneous fat necrosis, hypertension and nephrocalcinosis may be seen. Etiology include increased calcium absorption, familial hypercalcemic hypercalcuria, and hyperparathyroidism. Investigations should aim at measuring electrolytes and vitamin D and hormonal profile. Treatment is usually symptomatic. Loop diuretics may be helpful to excrete calcium.

Disorder Of Sexual Differentiation

Following fertilization, normal sexual development consists of three phases. The entire process starts by establishment of the genetic sex, followed by development of the gonads, and then a complex interaction of different hormones leading to developments of phenotypic sex. Any disturbances in the pathway may lead to disorder of sexual dysfunctions. This condition often sub classified in to three major categories.

1. *Overvirilized female (46 XX) or Female pseudo hermaphrodite*

   This is genetically female but has excess androgens in their body either due to increased endogenous production, or decreased metabolism or excess exposure. The increased productions are mostly due to enzyme defects in the steroid biosynthesis pathway, resulting congenital adrenal hyperplasia. This condition is usually because of 21 hydroxylase deficiency, resulting in blockage in the synthesis of cortisol, and overproduction of androgens resulting in virilization. Infants may present in shock, and an ambiguous genitalia. In another variety where the enzyme deficiency lies in 11 beta hydroxylase, cortisol production is in excess. Infants may present with hypertension and ambiguous genitalia. Diagnosis of these disorders is based on build-up of 17-hydroxyprogesterone in 21-hydroxylase deficiency and DOC and 11-deoxycortisol in 11beta-hydroxylase deficiency[6], in addition to chromosomal study and evaluation of internal genital organ by ultrasound scan that is required in all cases of DSD. Treatment includes correction of shock and electrolytes, and initiation of glucocorticoid and in some cases mineral corticoid therapy.

   In the second variety there is decrease metabolism of testosterone due to deficiency of the enzyme aromatase, which converts dehydroepiandrosterone (DHEA), an androgen to estrogen, resulting in excess of testosterone leading to virilization. In this case excess of androgens

cause virilization both in fetuses as well as in mothers.

In the third variety there is either excess of androgens produced by mother like in cases of ovarian or adrenal tumor in mother or by external exposure. In both the cases virilization in neonates should gradually disappear, as the exposure ceases.

2. *Undervirilized male (46XY)–Male pseudo hermaphrodite:*

   This is genetically male, and the condition develops due to errors in testosterone production, testosterone metabolism, and/ or end-organ action of testosterone. Defects in testosterone production may be due to deficiency of 17 alpha hydroxylase or 17, 20 lyase. This condition also blocks cortisol production and compensatory rise in ACTH level leading to hypertension. Neonates may present with salt wasting and shock. Elevation of precursors confirms the diagnosis. Therapy is aimed in stabilizing the infant and steroids as necessary.

   In other cases of undervirilized male there may be deficiency of 5 alpha reductase, which converts testosterone to functionally more potent DHT, or androgen insensitivity syndrome (AIS). Neonates presents with ambiguous genitalia with presence of male internal organs. Diagnosis is usually by genetic testing and measurement of testosterone levels. Sex assignment is often difficult in this cases, and a decision should be taken with parents on board.

3. *True hermaphrodites (Ovotestis) or the ovotesticular DSD.*

   Usually there is a mixture of mullerian and wolfian structures. There may be presence of both ovaries and testicles, or the gonads may be ovotestis, containing both ovarian and testicular tissues. Neonates usually have ambiguous genitalia, but sometimes female external genitalia is also possible. Diagnosis is ascertained by biopsy of the gonads. Treatment is mainly directed to removal of dysgenetic testicular tissue, and gender assignment.

Pituitary Dysfunction

Pituitary gland consists of two lobes anterior and posterior. Five different cell types in the anterior pituitary secrete six separate hormones: follicle-stimulating hormone (FSH), leutinizing hormone (LH), thyroid-stimulating hormone (TSH), growth hormone (GH), prolactin (PRL), and adrenocorticotropic hormone (ACTH). Alternatively, the posterior pituitary releases hormones important in the regulation of blood volume (arginine vasopressin [AVP]) and reproduction (oxytocin)[7].

Hypofunction of pituitary glands in neonatal period may be due to congenital abnormality such as septo-optic dysplasia, holoprosencephaly or may be due to genetic abnormalities such as mutation of PROP-1 gene. Newborns usually presents with short stature, recurrent hypoglycemia, and temperature instability. Mircopenis in a male child, in presence of hypoglycemiamay be a clue to the diagnosis. Often they have features of hypothyroidism, and even adrenal insufficiency. Hormonal estimation and MRI brain are necessary for diagnosis. Treatment is usually directed to specific hormonal supplementation.

Defects in posterior pituitary results in diabetes insipidus (DI), where infants present with dilute urine production in large quantities.Urine analysis show low specific gravity and MRI brain reveals absence of the bright spot (AVP). Treatment is by supplementing with desmopressin and careful monitoring of the fluid and electrolyte balance.

Conclusion

Endocrine problems in neonatal period is quite frequent and are mostly due to delay in the adaptation process. However serious endocrine issues may appear and at times can be life threatening. Pediatricians and neonatologist should be vigilant to pick up the clues and start the initial management before endocrinologists are consulted.

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Delayed Puberty

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Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics bounded by an age at which 95% of children of that sex & ethnic group have initiated sexual maturation. The clinical staging of puberty is performed by the criteria established by James Tanner. Children below 14 years of age do not require evaluation for delayed puberty.

Criteria:

Girls: No thelarche by 14 years

No menarche 5 years after thelarche

Boys: No increase in testicular volume by 14 years of age

Etiology of Delayed Puberty:

1. Constitutional delay in growth and puberty (CDGP)
2. Transient hypogonadotropic hypogonadism due to other causes:
   - Systemic disease
   - Malnutrition
   - Anorexia nervosa
   - Hyperprolactinemia
3. Hypogonadotropic hypogonadism
   - Kallman syndrome
   - Suprasellar tumours (eg. Craniopharyngioma)
   - GnRH receptor defect
   - CHARGE syndrome
   - CNS radiation/infection/surgery
4. Gonadal failure/ Hypergonadotropic hypogonadism
   - Congenital:
   - Gonadal dysgenesis
   - Chromosomal abnormalities – Turner syndrome, Klinefelter syndrome
   - Disorders of sex development – androgen insensitivity, 5 alpha reductase deficiency, Congenital Adrenal Hyperplasia (CAH).
   - Acquired: radiation, chemotherapy, autoimmune, infection, surgery

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Evaluation:

History:

Growth pattern - adolescents with CDGP have long standing history of short stature

General health – any symptoms of chronic ill health

Gonadal impairment – history of cryptorchidism, orchidopexy, irradiation

Sense of smell – Kallmann's syndrome

Family patterns – age at menarche, delayed growth spurt

CNS insult – radiotherapy, trauma, surgery, infection, birth asphyxia

Developmental delay – CHARGE syndrome, Prader Willi syndrome

Galactorrhea– hyperprolactinemia

Examinations:

Height, weight, BMI, parental heights

Pubertal staging

Dysmorphic features

Vitals with special reference to BP (CAH)

Neurological examination including fundus examination

Midline defects (hypopituitarism)

Pigmentation (steroidogenic defects)

Vitiligo, alopecia (autoimmune polyendocrinopathy)

Features of Turner/Klinefelter syndrome

Investigations:

1. Systemic diseases & nutritional disease: complete blood count, renal & liver function test, celiac screening, urine analysis.

2. Investigations related to disorders of gonadal axis:
   - Karyotyping – (Turner/Klinefelter syndrome)
   - Basal FSH & LH and serum estradiol/ testosterone&GnRH stimulation test

     Gonadotropin levels: after bone age more than 12 years

     FSH<2 mU/L– hypogonadotropic hypogonadism &> 10mU/L – hypergonadotropic hypogonadism

     FSH 2-10 mU/L – intermediate

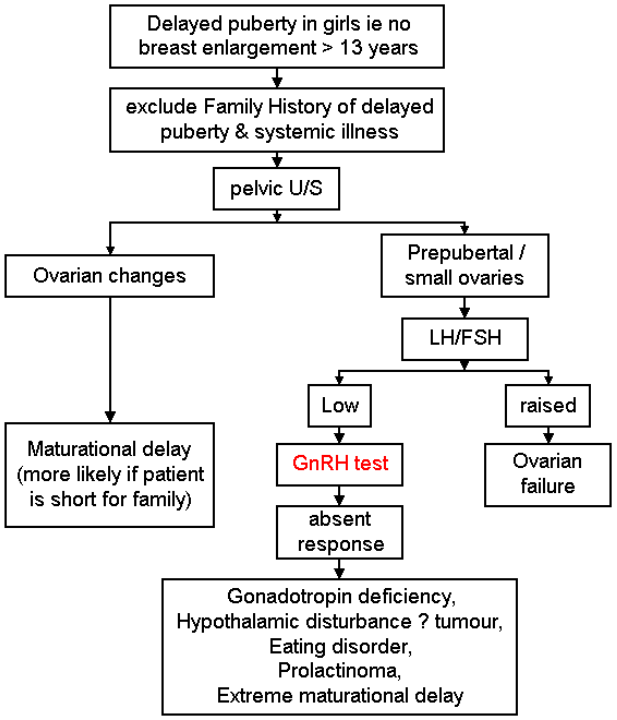
     GnRH agonist stimulation test: 100 microgram sc.

     Indication – indeterminate baseline gonadotropin levels

     LH & FSH at 0 min & 60 mins

     Exaggerated response – hypergonadotropic hypogonadism

     Blunted response – hypogonadotropic hypogonadism
   - Prolactin, insulin like growth factor
   - Pelvic ultrasound in girls
   - Bone age as established by wrist x-ray
   - MRI/CT scan of pituitary and surrounding structures



In boys:

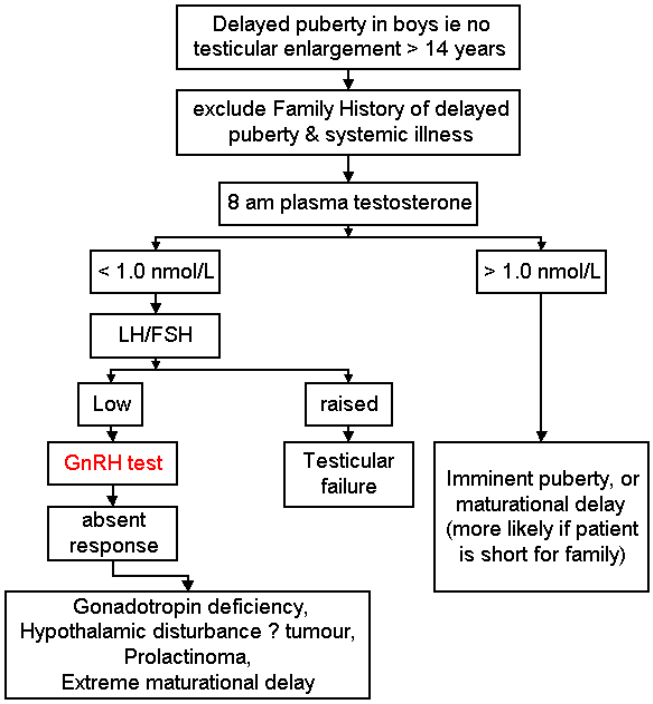
1. Differentiation of constitutional delay from permanent hypogonadotropic hypogonadism

   Clinical follow up after short course of testosterone

   Permanent hypogonadotropic hypogonadism –pubertal level of dehydroepiandrosterone sulfate: marker of adrenarche, blunted GnRH agonist stimulation test, human chorionic gonadotropin test (testosterone level <300ng/dl 48 hours after 4000IU/m2 IM HCG).

2. Hypergonadotropic hypogonadism:

   Karyotype & if karyotype normal, human chorionic gonadotropic stimulation test with steroid metabolites.



Management:

1.CDGP:

Medical treatment is often not necessary & monitoring may be sufficient. However, short courses with sex hormones may be allowed to prevent psychological sequelae.

Boys – bone age > 13 years

Injection of testosterone ester 100mg monthly for 3 doses (testosterone > 300 ng/ml 1 month after injection suggests CDGP)

Response is usually rapid & effective

Girls: gradually increasing dose of estrogen treatment with cyclical progesterone therapy once adequate estrogen therapy has been achieved.

2. Specific therapy:

systemic diseases, malnutrition, hyperprolactinemia, hypopituitaruism, celiac disease, steroidogenic defects, Turner's Syndrome.

3. Pubertal induction:

--Girls: bone age > 13 years

Gradually increasing estrogen dose till adult dose

Cyclical progesterone for withdrawal bleeding

Switch to combination oral contraceptive pills after adult dose achieved.

--Boys: bone age > 13 years

Injection testosterone ester 100 mg monthly for six doses & gradually increase till adult dose

4. Fertility management:

Girls:

Hypogonadotropic hypogonadism: cyclical hCG& human menopausal gonadotropin

Hypergonadotropic hypogonadism:

Ovarian extraction & cryopreservation: Turner syndrome

In vitro fertilization & embryo transfer

Boys: difficult to achieve, alternatives

Sperm donation

Testicular sperm extraction &intracytoplasmic sperm injection

Referral guidelines:

Children with delayed puberty need endocrine evaluation in the presence of: short stature, dysmorphism, developmental delay, normal screening investigations, arrest of pubertal development.

Approach to Precocious Puberty

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The term puberty is derived from the Latin word "Puberatum" which means age at maturity or adulthood . The onset of puberty is associated with an increase in the frequency and amplitude of gonadotrophin releasing hormone (GnRH) pulses ,which precedes the rise in luteinizing hormone (LH) and follicle stimulating hormone (FSH) .The age at onset is controlled by both genetic and extrinsic factors, and therefore may occur earlier or later than normal .The 4 -5 years of physiological variation in age at onset of puberty that is observed among normal individuals involves genetic factors ,ethnicity and environmental factors such as nutrition ,light ,stressors and endocrine disruptors.

Pubertal development is usually assessed by Tanner stages also known as sexual maturity rating (SMR). Tanner stage 1 is prepubertal ,whereas Tanner stage 5 is adult maturity . In boys , testis and penis development as well as pubic hair growth are assessed .In girls , breast development and pubic hair growth are assessed .In girls, puberty usually begins with breast development (thelarche) but occasionaly with the appearance of pubic hair (pubarche). Menarche usually occurs 2 years after breast development begins .In boys testicular enlargement (=4 ml) marks the onset of puberty and is followed by the appearance of pubic hair and development of external genitalia . The pubertal growth spurt is an early event in girls usually at Tanner stage B2 ,while in boys the growth spurt occurs late, usually at the time when a testicular volume of 10 ml is achieved .

The term precocious puberty signifies the appearance of the physical signs of puberty before the normal age for that gender and population. The onset of secondary sexual characters before the age of 9 years in boys and 8 years in girls is considered as precocious. Menarche before 9.5 years is also considered precocious. The timing of onset of puberty in girls has been decreasing all over the world.

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Etiology :

Depending on the primary source of the hormonal production, precocious puberty may be classified as Central also known as Gonadotrophin dependent precocious puberty (GDPP) or True and Peripheral also known as Gonadotrophin Independent precocious puberty (GIPP) or Precocious Pseudopuberty. In GDPP, there is premature activation of the hypothalamo–pituitary –gonadal(HPG) axis resulting in physical and hormonal changes of normal puberty, but at an early age and faster pace .It is always isosexual.In peripheral precocious puberty or GIPP,some of the secondary sex characteristics appear,but there is no activation of the normal hypothalamo-pituitary-gonadal(HPG) interplay. It may be isosexual or heterosexual(contrasexual).Peripheral precocious puberty, with late diagnosis and prolonged undertreatment , can induce maturation of the hypothalamo-pituitary-gonadal axis and trigger the onset of GDPP.GDPP is 5 times more common compared to GIPP .

Causes :

Central(CPP) or Gonadotrophin Dependent Precocious Puberty (GDPP) :

(a) Idiopathic (most common in girls)

(b) Hypothalamic hamartoma

(c) Tumors – Glioma, astrocytoma ,germ cell tumor

(d) CNS infection –Post meningitis, post encephalitis, neurotuberculosis

(e) CNS insults –trauma ,neurosurgery ,cranial irradiation ,perinatal asphyxia

(f) Malformations –Arachnoid cyst , hydrocephalus , septo-optic dysplasia ,neural tube defect ,neurofibromatosis

(g) Miscellaneous –Adoption,activating KISS1 and GPR 54 mutations,endocrine disruptor exposure

(h) Prolonged untreated GIPP – Congenital adrenal hyperplasia(CAH) ,McCune Albright syndrome(MAS),

Familial male limited precocious puberty(FMPP) .

Peripheral (PPP) or Gonadotrophin Independent Precocious Puberty (GIPP)Girls

A. Isosexual (feminizing)conditions :

McCune Albright Syndrome, Ovarian cyst

Ovarian tumors, Granulosa theca cell tumor

Feminizing adrenocortical tumor, Exogenous estrogen exposure

B. Heterosexual (musculinizing) conditions :

Congenital adrenal hyperplasia, Adrenal tumors

Ovarian tumors, Glucocorticoid receptor defect,

Exogenous androgen exposure

Boys

A. Isosexual(masculinizing) conditions :

Congenital adrenal hyperplasia, Adrenocortical tumor

Leydig cell tumor, Glucocorticoid receptor defect

Exogenous androgen Assocated with pseudohypo-parathyroidism

hCG secreting tumor – Familial male precocious puberty

Central nervous system

Hepatoblastoma

B. Heterosexual (feminizing) conditions :

Feminizing adrenocortical tumor

SCTAT associated with PeutzJeghers Syndrome

Exogenous estrogens

Incomplete(Partial) precocious puberty :

(a) Premature thelarche

(b) Premature adrenarche

(c) Premature menarche

Peripheral precocious puberty can induce maturation of the hypothalamo–pituitary-gonadal(HPG) axis and trigger the onset of central precocious puberty .This mixed type of precocious puberty occurs commonly in congenital adrenal hyperplasia(CAH), McCune Albright Syndrome(MAS) and Familial male limited precocious puberty(FMPP) .

Some benign conditions such as premature thelarche and premature pubarche may mimic precocious puberty.Premature thelarche refers to isolated breast development before the age of 8 yr.This is typically seen in girls below 3 yrs.Premature pubarche refers to isolated appearance of sexual hair in children younger than 7-8 yrs. This is usually benign and non-progressive .

Clinical manifestations :

Sexual development may begin at any age and generally follows the sequence observed in normal puberty in cases of GDPP. In girls early menstrual cycles may be more irregular than they are in normal puberty .The initial cycles are anovulatory but pregnancy has been reported as early as 5.5 yrs of age .In boys ,spermatogenesis has been observed as early as 5-6 yrs of age.In affected girls and boys,height,weight and osseous maturation are advanced.The increased rate of bone maturation results in early closure of the epiphyses.Without treatment, approximate 30 % of girls and an even larger percentage of boys achieve a height less than 5th percentile as adults .Mental development is usually compatible with the chronological age .Emotional behavior and mood swings are common, but serious psychological problems are rare .

Although the clinical course is variable,3 main patterns of pubertal progression can be identified in GDPP.Most girls (particularly those younger than 6 yr of age at onset and large majority of boys have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to loss of height potential . An increasing percentage of girls (older than 6 yr of age at the onset with an idiopathic form have slowly progressive variant ,characterized by parallel advancement of osseous maturation and linear growth,with preserved height potential.Spontaneously regressive or unsustained central precocious puberty(CPP) is quite rare .

Assessment of Precocious Puberty :

History :

Age at onset – Idiopathic GDPP, the most common cause of central precocity , usually presents between 6 to 7 yrs of age .Younger the onset of puberty; more is the chance of finding a significant underlying disorder .Girls with McCune Albright syndrome(MAS) present at around 3 yrs with precocious puberty and vaginal bleeding has been reported in babies as young as 4 months . Boys with FMPP present within the first few years of life with progressive secondary sexual characters and rapid linear and bone growth .Non classic CAH may present at any age with advanced physical growth ,bone age and precocity .

Sex – GDPP is 5-10 times more common in girls than boys. GDPP in girls is most often idiopathic (75 -90 %) whereas secondary CNS pathology is found in two third of boys .

Pubertal progression – The chronology of the appearance of secondary sexual characters and the pace of pubertal

progression should be recorded .

Family history – Details of timing and sequence of puberty in parents and siblings should be taken .Precocious puberty in boys and genital ambiguity in girls of the same family would suggest CAH .A family history of precocious puberty limited to males would suggest familial testotoxicosis (FMPP).

Evidence of linear growth acceleration should be noted .Precocity is associated with growth spurt, exception to the rule being hypothyroidism and sellar mass with growth hormone deficiency.Incomplete precocious is different from precocious puberty by the absence of other signs of puberty and a normal growth rate .

Headache, vomiting ,visual disturbance ,proptosis and field defects would suggest intracranial SOL .

History of perinatal events, developmental milestones, neurologic involvement should be taken. Girls with cerebral palsy start puberty earlier than normal girls ;but menarche may be delayed .Gelastic seizures points toward hypothalamic hamartoma .

Adoption :Danish studies showed that internationally adopted children are 10-20 times more likely to develop precocious puberty .

Symptoms suggestive of hypothyroidism should be looked for.

Possibility of sexual abuse ,foreign body or vaginal infection must be probed in girls with isolated menarche .

Administration of exogenous steroids in the form of pills,creams and syrups should be enquired .

Physical Evaluation :

- Measurements of height ,weight , and height velocity (cm/yr) .
- Measurement of BMI is important since obesity leads to early sexual maturation ,especially in girls .
- Pubertal staging according to Tanner's staging .
- The first sign of GDPP in girls is enlargement of breasts,which may be unilateral to begin with. Pubic and axillary hair appear simultaneously or soon after breast enlargement .Menarche is often a late event .Pubertal growth spurt occurs early in girls .
- The earliest evidence of GDPP in boys is enlargement of testes. Pubertal onset is confirmed if the length of the testes in their long axis is more than 2.5 cm or volume is more than 4 ml . Other signs of puberty such as reddening and thinning of scrotum and growth of pubic and axillary hair may be present. In GIPP, early penile and pubic hair growth is seen without testes enlargement; penile length is out of proportion to testicular size .Unilateral enlargement of testis denotes underlying testicular malignancy like Leydig cell tumor .
- Look for –

  (i) Androgen effect : acne,hirsutism ,increased muscle mass and cliteromegaly and

  (ii) Estrogen effects : breast development and changes in vaginal mucosa. A glistening red appearance of vaginal mucosa is consistent with non estrogen stimulated mucosa, whereas a pink mucosa with mucus indicates estrogen stimulation .
- Café au lait macules are characteristic of McCune Albright Syndrome and neurofibromatosis .
- Neurological examination should include fundus examination and perimetry .
- Examination for signs of hypothyroidism .
- Hypertension :Seen in CAH due to 11 ß hydroxylase deficiency and in adrenal tumors .

Investigations :

Bone age :

It is a reliable and quick method to assess the pubertal growth. In GDPP, bone age is advanced by more than 2 yrs .Skeletal maturation is advanced in all cases of precocious puberty – except if associated with hypothyroidism .It remains normal in incomplete forms .

Hormonal evaluation :

Serum luteinizing hormone – Basal LH is the best screening test to diagnose GDPP. LH level less than 0.1 IU/L by a very sensitive assay indicates prepubertal stage .Serial measurement of LH in blood samples obtained during sleep has better diagnostic accuracy than that of a single random sample . A definitive diagnosis of GDPP is made by performing stimulation tests using GnRH or GnRHanalog(leuprolide).

Serum testosterone – Measurement of early morning serum testosterone is preferred in boys. Testosterone levels are very high in tumors.Pubertal testosterone level with suppressed gonadotrophins are seen in FMPP .

Serum estradiol – Estradiol measurements are less reliable. The level may fluctuate from week to week and may be low in early phases of the disease. A value of more than 20 pg/ml is suggestive of puberty .If the levels are more than 100 pg/ml, an ovarian cyst or tumor should be suspected .Estradiol levels are markedly elevated in MAS .

Free t4 and TSH – Indicated if there is poor growth or large ovarian cyst .

Serum prolactin : It may be helpful if there is growth arrest and galactorrhea .

Growth hormone – GH and IGF 1 studies are indicated if there is associated short stature .

DHEA and DHEAS – Dehydroepiandrosterone and dehydroepiadrosterone sulphate are elevated in premature pubarche and very high in virilizing adrenal tumors .

Serum 17 hydroxyprogesterone – it helps to confirm 21 hydroxylase deficiency especially non classic CAH and 11 ß hydroxylase deficiency

Serum/CSF hCG – Elevated in hCG secreting tumor in boys .

Serum AFP : alpha fetoprotein is elevated in hepatoblastoma.

Imaging studies :

MRI brain – High resolution MRI of brain is indicated especially in young boys. It demonstrates enlargement of the pituitary gland ,and serious CNS pathology such as glioma or astrocytoma . Hamartoma appears as pedunculated or sessile mass usually attached to posterior hypothalamus between tuber cinereum and mammillary bodies .

Pelvic ultrasonogram – To evaluate the size and morphology of the uterus and ovaries .The earliest feature of estrogenization of the uterus is a change in the shape of the uterus from prepubertal tubular shape to pubertal pear shape .An endometrial thickness of 6-8 mm suggests imminent menarche .The pubertal ovarian volume is usually above 3 ml. Bilaterally enlarged ovaries with multiple cysts (>6 cysts) which are greater than 4 mm diameter are characteristic. Larger cysts are seen in premature thelarche(<3 cysts),thelarche variants(3-6 cysts),hypothyroidism and MAS .

Testicular ultrasonogram helps to diagnose testicular tumors like Leydig cell tumors and adrenal rest tumors .

CT or MRI of pelvis and abdomen : These are helpful to rule out adrenal or ovarian causes of precocious puberty in girls and testicular causes in boys .Unilateral or asymmetric enlargement of ovaries or adrenal glands indicates tumors and cysts .In MAS ,ovaries are asymmetric with large unilateral ovarian cysts .

Bone scan and skeletal survey are helpful in MAS to detect polyostotic fibrous dysplasia .

Management :

Specific management is indicated for an underlying treatable clinical condition such as brain ,ovarian or adrenal tumor .Hypothalamic hamartoma does not require surgical management unless the lesion is pedunculated . The child with premature thelarche should be followed up every 3-4 months for at least 2 yrs .

Management of GDPP :

Treatment of progressive CPP is indicated if

(a) Predicted adult height is less

(b) Psychologically distressing to the child

(c) Progress is rapid

GnRHanalogs(GnRHa) are the only effective and safe treatment for GDPP at present. Administration of GnRHa produces continuous stimulation of pituitary instead of the normal physiological pulsatile stimulation . The long term effect of constant dosing is down regulation of responsiveness resulting in fall in gonadotrophin levels and subsequently reduction of sex steroids to prepubertal levels .

Both rapid acting and depot preparations are available in Indian market but depot forms are generally preferred because of convenience and good compliance .These include leuprolide(3.75 mg),triptorelin(3.75 mg) and goserelin(3.6 mg).A dose of 3.75mg is administered every 28 days and doses are adjusted depending on hormonal suppression . Extended release preparations of leuprolide and triptorelin(11.25 mg, given every 3 mo) and goserelin (10.8

Follow up protocol of GDPP on GnRHanalogs :

Follow Up Details	Time Intervals	Expected Outcome
Growth velocity	3-6 mo	< 5 cm/yr
BMI	3-6 mo	Static
Tanner breast stage (girls)	3-6 mo	Static or regression
Testicular volume(boys)	3-6 mo	Static or regression
Bone age and predicted adult height	At 6 mo ;then yearly	Slow progression
Basal /stimulated LH levels	At 6-8 wk;at 6 mo;then yearly	Suppression ;decrease to <1 IU/L
Testosterone/estrogen levels	At 6 mo; then yearly	Decrease to prepubertal level Testosterone<10-20ng/dl in boys ;Estradiol <5-10 pg/ml in girls
Bone mineral density	yearly	Mild delay/normal

mg every 3 mo) have proven to be equally effective .

These drugs should be given according to prescribed dose at specified time intervals. There will be stimulation instead of suppression , if recommended dosage interval is not adhered to. In girls,breast size may regress, menses ceases and vaginal mucosa becomes nonestrogenized. In boys,testicular volumes remain static or decrease and genital growth regresses .Treatment results in decrease in growth velocity and osseous maturation .If the clinical response is suboptimal,complete reevaluation of the case should be done .

Medroxyprogesterone (100mg/m^2/d) or cyproterone acetate (70-100 mg/d) can be combined with GnRHa during the first 3 mo of treatment to avoid initial flare up response .Adjunct therapies like aromatase inhibitors, anti-androgens and sex steroids are being tried along with GnRH analogs for various indications .GH therapy is indicated if there is GH deficiency along with precocious puberty .

Sterile abscess is the commonest adverse reaction followed by headache and hot flashes due to hypoestrogenism. Discontinuation of therapy is based on chronological age,bone age,growth velocity,final expected height and psychological condition of the child .Discontinuation at a chronological age of 11 yr and bone age of 12 yr has been associated with maximum adult height and menarche at normal population norms.The effects of GnRH analogs are reversible on discontinuation of therapy with restoration of normal function within 3 mo after stopping treatment .

Management of GIPP :

Treatment of GIPP is more challenging than treatment of GDPP .Surgery is the treatment of choice for adrenal ,ovarian and testicular tumors .Functional ovarian cysts are followed up since spontaneous regression is common. Medroxyprogesterone acetate, given in a dose of 100 mg/m^2 every 2 wk ,inhibits secretion of pituitary gonadotrophins and reduces the effect of LH. It is comparatively cheap .Cyproterone acetate is used in some centers.

Glucocorticoid treatment is effective in CAH .Growth hormone or aromatase inhibitors are often given along with glucocorticoids to stimulate linear growth.Thyroxine is the treatment of choice for precocious puberty secondary to hypothyroidism .In patients with autonomous gonadal steroid production such as MAS and FMPP , therapy is aimed at reducing sex steroid production or its effects,thereby arresting growth acceleration and pubertal progression. Combinations of cyproterone and ketoconazole;bicalutamide and anastrozole as well as testosterone and spironolactone have been used in FMPP with variable success .

Psychological support :

Psychological support for the child and parents is an essential part of the general management scheme .The child's psychological development corresponds with the chronological age . No major psychopathology is associated with precocious puberty .

Conclusion :

Precocious puberty ia an alarming experience for the family . With detailed medical history and complete physical examination ,one should be able to classify precocious puberty and reach its probable etiology .Early diagnosis helps to identify the underlying organic brain disorder in children with central precocious puberty and institute appropriate management .GnRH agonist therapy is both safe and effective .Peripheral precocious puberty is caused by secretion of sex hormones either from the gonads or adrenal glands . Treatment is directed at the underlying pathology .Incomplete precocity is a variant of normal puberty,requires no interventions ,only periodic follow up is necessary .

The drugs commonly used in the management of GIPP are listed below -

Drug-class	Drug –Name	Action	Dosage schedule	Adverse effects
Antifungal agents	Ketoconazole	Inhibits steroid synthesis at the level of 17α hydroxylase	10-20 mg/kg/d 8 hourly	Hepatotoxicity, Low cortisol
Anti-androgens	Spironolactone Bicalutamide	Blocks the effect of testosterone and dihydrotes-tosterone at the androgen receptor	SL :60 mg/m^2/d 12 hourly BC :2 mg/kg/day	Gynaecomastia, Urinary frequency
SERM (Selective Estrogen Receptor, modulator)	Tamoxifen	Produce estrogen antagonist activity	20 mg once a day	Hypercalcemia, Hypertriglyceridemia
Anti estrogens	Fulvestrant	Pure estrogen antagonist	Monthly IM depot 4mg/kg	Hot flashes,edema , ,vaginal bleeds
Aromatase inhibitors	Testolactone(TL) Anastrozole(AZ) Letrozole(LZ)	Inhibits the action of aromatase which converts androgen to estrogen	TL :20-40mg/kg/d 6 hourly AZ:0.1-0.2 mg/kg/d LZ :2.5 mg once daily	TL : alopecia, fractures AZ :Fracture,hot flashes

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A Short Trip to Insulin

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Children with type 1 diabetes mellitus (T1DM) require proper insulin therapy,regular monitoring of blood glucose(including HbA1c) and an optimal diet . Insulin therapy began with beef/ pork insulin, followed by an era of recombinant human insulin and now we are in the third phase of insulin therapy where insulin analogues are being used .

Insulin

Chemistry :

Insulin is a peptide hormone, containing two amino acid chains (subunit A contains 21 amino acids and subunit B contains 30 aminoacids), linked by disulphide bonds. It is secreted from the ß cell of the islet of Langerhans of pancreas. In solution, insulin can exist as a monomer ,dimer ,or hexamer . Two molecules of Zn2+ are coordinated in the hexamer, and this form of insulin presumably is stored in the ß cell granules. As the concentration falls to physiological levels ,the hormone dissociates into monomers, which likely are the biologically active form .Insulin is a member of the insulin-like growth factor(IGF) family .IGF1 and IGF2 have similar structure to that of proinsulin except that the Cpeptide are not removed in the mature protein .

Regulation of insulin secretion :

Insulin secretion is tightly regulated to maintain stable concentrations of glucose in blood during both fasting and feeding . This regulation is achieved by the coordinated interplay of various nutrients ,G I hormones, pancreatic hormones and autonomic neurotransmitters. Glucose, amino acid, fatty acid, ketone body stimulate insulin secretion. In general ,any condition that activates the sympathetic nervous system (e.g. hypoxia, hypoglycemia, exercise ,hypothermia ,surgery or severe burns) suppresses the secretion of insulin by stimulation of alfa 2 adrenergic receptors. Predictably , alfa 2 adrenergic receptor antagonists increase basal concentrations of insulin in plasma, while ß2 adrenergic receptor antagonists decrease them .

Glucose provokes insulin secretion more effectively when taken orally than when administered intravenously because the oral route induces the release of GI hormones(GIP, GLP-1) and stimulates vagal activity . Glucose enters the ß cell by facilitated transport mediated by the specific glucose transporter, GLUT2 .Glucose induced insulin secretion is biphasic: the first phase reaches a peak after 1-2 minutes and is short lived; the second phase has a delayed onset but longer duration .The plasma t1/2 of insulin normally is 5-6 minutes but may be increased in diabetics who develop anti insulin antibodies . Cpeptide is secreted in equimolar amounts with insulin ,but its molar concentration in plasma is higher because of its considerably longer t1/2. Degradation of insulin occurs primarily in liver, kidney and muscle .Key insulin target tissues for regulation of glucose homeostasis are liver, muscle and fat. Insulin stimulates intracellular use and storage of glucose,amino acids and fatty acids and inhibits catabolic processes such as the breakdown of glycogen, fat, protein .

Virtually all forms of DM result from a decrease in the circulating concentration of insulin(insulin deficiency) and/or a decrease in the response of peripheral tissues to insulin (insulin resistance).These abnormalities lead to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids; the central feature of the syndrome is hyperglycemia.

In both types of diabetes, glucagon (elevated in untreated patients) opposes the hepatic effects of insulin by stimulating glycogenolysis and gluconeogenesis but has relatively little effect on peripheral glucose utilization. Thus, in the diabetic patient (depressed insulin signaling and hyperglucagonemia), there is increased hepatic glucose production, decreased peripheral glucose uptake, and decreased conversion of glucose to glycogen in the liver.

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Hypoglycemic actions of Insulin :

Liver	Muscle	Adipose tissue
Inhibits hepatic glucose production(decreases gluconeogenesis and glycogenolysis) Stimulates glucose uptake	Stimulates glucose uptake Inhibits flow of gluconeogenic precursors to the liver (alanine,lactate, pyruvate)	Stimulates hepatic glucose uptake Inhibits flow of gluconeogenic precursor to liver(glycerol) and reduces energy substrate for hepatic gluconeogenesis

Alterations in insulin and glucagon secretion also profoundly affect lipid, ketone, and protein metabolism.Normally, insulin inhibits lipolysis, stimulates fatty acid synthesis . Conversely, glucagon stimulates ketone body production by increasing fatty acid oxidation and decreasing concentrations of malonyl CoA. In patients with type 1 DM, insulin deficiency and glucagon in excess provide a hormonal milieu that favors ketogenesis and may lead to ketoacidosis.

Insulin also enhances the transcription of lipoprotein lipase in the capillary endothelium. Thus, hypertriglyceridemia and hypercholesterolemia often occur in untreated or undertreated diabetics. In addition, insulin deficiency may be associated with increased production of VLDL.

Insulin Therapy :

Insulin is the mainstay for treatment of virtually all type 1 DM and many type 2 DM patients. When necessary, insulin may be administered intravenously or intramuscularly; however, long-term treatment relies predominantly on subcutaneous injections of the hormone. Insulin preparations are classified according to their duration of action into rapid, short, intermediate, and long acting and by their species of origin—human or porcine. Human insulin is widely available, as is porcine insulin, which differs from human insulin by one amino acid (alanine instead of threonine in position B30). Human insulin, produced using recombinant DNA technology, is more water soluble than porcine insulin owing to the presence of an extra hydroxyl group. The vast majority of preparations now are supplied at neutral pH, which improves stability and permits storage for several days at room temperature.

A .Conventional insulin therapy :

Conventional therapy, the most commonly used, refers to 1-2 daily insulin injections. The total daily dose is divided into 2/3 pre-breakfast and 1/3 pre-dinner. Ratio of short acting (human regular): intermediate acting (NPH) = 30:70. Insulin is started at 60-70% of the full replacement dose. Further adjustments are made as per pre-meal sugars. After initial stabilization of blood glucose the patient does not alter the daily dose of insulin as per premeal sugars, exercise and expected diet.

B. Intensive insulin therapy (IIT) :

Intensive therapy includes the administration of insulin =3 times daily by multiple daily injections (MDI) or pen, or an external pump. Every dose of insulin is adjusted according to the pre-meal blood glucose(performed at least four times daily), dietary intake, and anticipated exercise. It does not refer to the type of insulin. Total daily dose is divided as follows:

Basal dose:

25-30% of the total dose in toddlers and 40-50% in older children, given at bedtime. This suppresses the glucose production between meals and overnight.

Bolus dose:

Remaining dose is divided into 3 pre-meal doses. The meal time (prandial) doses limit post-prandial hyperglycemia. Every bolus dose of insulin is adjusted as per the scale. Sliding scale refers to basing an insulin dose as per the pre-meal sugars. Thinking scales are replacing this concept, where the amount of exercise (recent and expected) and the expected diet intake are also taken into consideration along with the pre-meal sugars.

Subcutaneous Insulin dosing :

Age (yr)	Target premeal Blood glucose(mg/dl)	Total daily Insulin(U/kg/d)	Basal insulin, % of total daily dose	Bolus insulin	
				Units added per 100mg/dl above target	Units added per 15 gm at meal
0-5	100-200	0.6-0.7	25-30	0.50	0.50
5-12	80-150	0.7-1.0	40-50	0.75	0.75
12-18	80-130	1.0-1.2	40-50	1.0-2.0	1.0-2.0

Newly diagnosed children in the "honeymoon" may only need 60-70% of a full replacement dose .

IIT imposes extra demand on the family in terms of number of injections per day, blood glucose monitoring and financial costs. Diabetes control and complications trial (DCCT) has conclusively proven that intensive therapy improves long-term glycemic control (HbA1c) and reduces the risk of development and progression of microvascular complications; the major drawback being 2-3 fold increase in severe hypoglycemic episodes. Dose adjustment for normal eating (DAFNE) trial has shown that, a flexible IIT combining dietary freedom and insulin adjustment, significantly improves glycemic control at 6 months .

Therefore, American Diabetes Association (ADA) guidelines for treatment include a contraindication for implementing tight metabolic control in infants younger than 2 years old and an extreme caution in children of 2–7 years of age in whom hypoglycemia may impair brain development. Current therapies for type 1 and type 2 DM therefore aim for tight metabolic control, always keeping in mind the risks of severe hypoglycemia in individual patients.

C. Types of insulin :

The pharmocokinetic details of available insulins are shown in following table. Conventional insulins were beef/pork pancreas extract. Intermediate/long acting preparations were prepared by adding zinc (Lente, ultralente) or other proteins e.g., protamine (NPH). Recombinant human insulin has lesser antigenic reactions and side effects, better subcutaneous absorption, earlier and a more defined peak, and have replaced older insulins. Modifying the amino acid sequence of insulin molecule has developed newer analogues.

Short and Rapid acting Insulin:

Traditionally, the short-acting insulins were solutions of regular, crystalline zinc insulin dissolved in a buffer at neutral pH. These preparations have a rapid onset of action but short duration. More recently, modified recombinant insulins have been introduced with even more rapid onset and shorter duration of action; they therefore are termed "rapid acting"insulins. Short-acting (i.e., regular) insulin usually is injected subcutaneously 30–45 minutes before meal,and also may be given intravenously or intramuscularly. Regular insulin typically is given subcutaneously, often in combination with an intermediate or long-acting preparation. Special buffered formulations of regular insulin are available for use in subcutaneous infusion pumps .

Lispro, aspart and glulisine are the available insulin analogues.These analogues are absorbed three times more rapidly from subcutaneous sites than is human insulin. Consequently, there is a more rapid increase in plasma insulin concentrations and an earlier hypoglycemic response. Injection of the analogues 15 minutes before a meal affords glycemic control similar to that from an injection of human insulin given 30 minutes before the meal. Owing to their fast onset, the rapid-acting insulin analogues all may be injected immediately before or after a meal. Factors such as gastroparesis or anorexia may cause many diabetic patients to eat fewer calories than anticipated. Due to their pharmacokinetics, the rapid-acting analogues may be

Property of Insulin preparations:

Type	Name	Appearance	Added protein	Buffer	Action, hours		
					Onset	Peak	Duration
Rapid Acting	Lispro	Clear	None	Phosphate	0.25	0.5-1.5	0.25
	Aspart	Clear	None	Phosphate	0.25	0.6-0.8	3-5
	Glulisine	Clear	None	None	–	0.5-1.5	1-2.5
Short acting	Regular Soluble	Clear	None	None	0.5-0.7	1.5-4	5-8
Intermediate	NPH(Isophane)	Cloudy	Protamine	Phosphate	1-2	6-12	18-24
	Lente	Cloudy	None	Acetate	1-2	6-12	18-24
Slow/Long Acting	Ultralente	Cloudy	None	Acetate	4-6	16-18	20-36
	Protamine zinc	Cloudy	Protamine	Phosphate	4-6	14-20	24-36
	Glargine	Clear	None	None	2-5	5-24	18-24
	Detemir	Clear	None	Phosphate	1-2	4-14	6-24

administered postprandially based on the amount of food actually consumed, possibly providing smoother glycemic control and decreasing the risk of hypoglycemia.

Relative to regular insulin, the prevalence of hypoglycemia is reduced by 20–30% with insulin lispro, and glucose control, as assessed by Hb A1c .Insulin aspart is formed by the replacement of proline at B28 with aspartic acid. In clinical trials, insulin aspart and insulin lispro have had similar effects, with lower rates of nocturnal hypoglycemia as compared with regular insulin.

A third rapid-acting insulin analog, insulin glulisine with kinetics similar to insulin aspart and lispro , is available for use in the U.S. Insulin glulisine also is FDA-approved for continuous subcutaneous insulin infusion (CSII) pump use.

Intermediate acting insulin:

These insulins are formulated to dissolve more gradually when administered subcutaneously;thus, their durations of action are longer. The two preparations used most frequently are Neutral Protamine Hagedorn (NPH) / isophane insulin and lente insulin (insulin zinc suspension). NPH insulin is a suspension of insulin in a complex with zinc and protamine in a phosphate buffer. Lente insulin is a mixture of crystallized (ultralente) and amorphous (semilente) insulins in an acetate buffer, which minimizes the solubility of insulin.Human insulin has a more rapid onset and shorter duration of action than does porcine insulin.Intermediate-acting insulins usually are given either once a day before breakfast or twice a day .In patients with type 2 DM, intermed iate-acting insulin given at bedtime may help normalize fastingblood glucose. When regular insulin is combined with NPH or Lente ,the composite profile poorly mimics normal endogenous insulin secretion .Lente insulin has been discontinued and are no longer available .

Long acting insulin :

Ultralente insulin and Protamine zinc insulin : These are no longer used and available .

Insulin Glargine: It is less soluble at neutral pH because of shift in the isoelectric point from pH 5.4 to 6.7. It is supplied as a clear solution at acidic pH. After injection, the acid in the vehicle is neutralized and glargine precipitates, thereby delaying absorption and prolonging action. Studies comparing insulin glargine versus NPH insulin have consistently shown significantly lower fasting plasma glucose and a significant decrease in the variability of fasting blood glucose values in glargine pooled groups. Insulin glargine can be used in combination with various oral hypoglycemic agents like sulphonylurea and/or metformin .

Insulin Detemir: Insulin detemir has a more predictable, protracted and consistent effect on blood glucose than NPH insulin. It is as effective as NPH insulin in maintaining overall glycemic control, with a similar/lower risk of hypoglycemia. It should not be mixed with any other insulin preparations .Insulin detemir is, therefore, a promising new option for basal insulin therapy.

Insulin injection :

Where to inject ?

Insulin is injected into the subcutaneous tissue of the upper arm, anterior and lateral aspects of the thigh, buttocks and abdomen .insulin is absorbed more rapidly from the abdomen>arm>thigh>buttock .rotating within one area recommended rather than rotating to a different area with each injection because it decreases day to day variability in absorption .more consistency in insulin levels may be obtained by giving all shots in the same parts for a week at a time e.g. in the arm area for a week and then in the leg sites for a week or choose one area for the morning and one for the evening .exercise increases the rate of absorption from injection sites .

How to draw ?

Draw an amount of air equal to the dose of insulin required and inject into the vial to avoid creating a vacuum .when both short acting and long acting insulin are to be given ,draw the short acting insulin followed by long acting insulin .

How to inject ?

Grasp a fold of skin between the thumb and index finger and push the needle at 90^0 angle and the needle should be embedded within the skin for 5 sec after complete depression of the plunger to ensure complete delivery .Release the pinch before injecting or else insulin will be squeezed out

How to store ?

Vial should be refrigerated and warmed to room temperature to limit local irritation at the injection site. Extreme temperatures(<2 or 30^0C) and excess agitation should be avoided to prevent loss of potency, clumping, frosting ,or precipitation. Patients should always have available a spare bottle of each type of insulin used .

D. Modalities of injectable Insulin delivery :

Continuous Subcutaneous Insulin Infusion (CSII):Continous subcutaneous insulin infusion (CSII) via battery powered pumps provides a closer approximation of normal plasma insulin. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the insulin to carbohydrate ratio and the correction scale for pre-meal glucose levels . The patient can enter the patient's blood glucose level and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin

bolus dose .The advantages of pumps are that multiple daily doses are not required, decreased nocturnal hypoglycemia and improved control of Dawn's phenomenon with the use of variable basal rate and better freedom in timings of meals and snacks.

Insulin pen injectors:

Premixed insulin preparations in pen syringes maintain glycemic control. They are small and convenient, use smaller gauge needles and can facilitate compliance. They are preferred by patients, more discreet for use in public, overall easier to use, insulin dose scale on the pen is easier to read. The use of premixed insulin decreases the errors that occur while mixing the insulins and also the contamination if any.

E. Noninvasive insulin delivery:

There is a long history of attempts to develop novel routes of insulin delivery that are both clinically effective and tolerable. However, despite significant research, the first effective noninvasive delivery systems for insulin are only now in development, marking a new milestone in effective management of diabetes. It does appear that the most clinically viable system to date may be pulmonary delivery .

Intradermal approach :

Jets:

These devices administer insulin without needles by delivering a high-pressure stream of insulin into subcutaneous tissue. The discomfort associated is the same as with insulin injections. Insulin is absorbed faster and hence glycemic control can be altered. It should not be viewed as a routine option but may benefit selected cases; such as those with severe insulin-induced lipoatrophy or phobia for needles. They are rather expensive.

Transferosomes:

These are lipid vesicles made of soybean phosphatidylcholine loaded with insulin that are flexible enough to pass through pores much smaller than themselves, despite being much larger. Transferosomes transport the insulin with at least 50% of the bioefficiency of a subcutaneous injection. These are not rapid enough for bolus regimen but useful for basal regimen. The application of insulin-laden transferosomes over a skin area 40 cm^2 would provide the daily basal insulin needs.

Intranasal approach :

Intranasal insulin have a low bioavailability and the dose needed for glycemic control is 20 times higher than that of subcutaneous administration. Permeability enhancers (lecithin, laureth-9) are incorporated in most nasal formulations to augment the low bioavailability. High rate of treatment failure and propensity to cause nasal irritation makes them a less feasible option.

Buccal :

A buccal system delivering a liquid aerosol formulation of insulin via a metered dose inhaler has been developed . The buccal insulin preparation is human recombinant insulin with added enhancers, stabilizers, and a non-chlorofluorocarbon propellant. Data on efficacy and adverse effects is still limited.

Inhaled insulin :

Lung is an ideal route for the administration of insulin due to a vast and well-perfused absorptive surface. Action after inhalation is 15 to 20 min. The FDA approved inhaled insulin for use in patients with type 1 or type 2 DM. This powdered formulation of recombinant human insulin is inhaled through the mouth before eating using a special inhalation device. Although the efficacy of inhaled insulin is more clearly documented for patients with type 2 DM, approval also was given for use in subjects withtype 1 DM. Some concerns have been expressed about the use of the inhaled formulation inpatients with chronic obstructive pulmonary disease and asthma.

Gastrointestinal delivery:

Hexyl-insulin monoconjugate 2 (HIM2) is recombinant insulin with a small polyethylene glycol 7-hexyl group attached to protein 828 amino acid lysine. Theoretical advantage that it would mimic the enterohepatic circulation of endogenous insulin is limited by low bioavailability and extensive degradation in the gut mucosa .

Adverse reactions :

a. Hypoglycemia

b. Insulin allergy and resistance

c. Lipoatrophy and Lipohypertrophy

d. Insulin edema

KEY MESSAGES

(a) Improved glycemic control requires early and prolonged implementation of intensive insulin therapy. Psychological and economic demand is the major constraint in the Indian perspective.

(b) Pen injectors appear to be a more feasible option to MDI, whereas CSII is useful only in some special situations.

(c) All diabetics would need a short course teaching flexible intensive insulin treatment.

(d) The cost -benefit ratio of short acting insulin analogues in the treatment of diabetic patients is still unclear.

(e) All diabetic patients who receive insulin should be aware of the symptoms of hypoglycemia, carry some form of easily ingested glucose, and carry an identification card or bracelet containing pertinent medical information .

Normal Menstruation And Common Menstrual Problems In Adolescent Girls Including PCOS

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Menstruation is the visible manifestation of cyclical physiologic uterine bleeding due to shedding of the endometrium as a result of invisible interplay of hormones mainly through hypothalamo-pituitary-ovarian axis. The ovary responds to FSH and LH in a defined, sequential manner to produce follicular growth, ovulation and corpus luteum formation. In the early menstrual cycle the ovary produces estrogen, which is responsible for endometrial growth. Following ovulation, progesterone is also produced in significant quantities, which transforms the endometrium into a form ideal for implantation of the embryo. When pregnancy does not occur, the ovary ceases to produce estrogen and progesterone, the endometrium is sloughed and the cycle begins again. Average age of menarche is 13 years. A normal menstrual cycle lasts from 21 to 35 days with two to six days of flow and an average blood loss of 20 to 60 ml.

Parameters for Normal Menstrual Cycles in Adolescents[1]

	Normal
Menstrual Cycle Frequency	21-45 days
Cycle Variation from cycle to cycle	Less than in adults
Duration of flow	4-8 days
Volume of flow	4- 80 ml

Menstrual abnormalities in adolescents

Dysmenorrhoea :

This is a common problem in adolescent girls. At the start of menarche, the cycles may be painless as they are anovulatory. With the onset of ovulation, dysmenorrhea is an increasingly common problem, with spasmodic and colicky pain beginning premenstrually and lasting until day two-three of the cycle. Pain affects the lower abdomen and back and occasionally radiates to the thighs. In severe cases, nausea, vomiting and diarrhea may be experienced. The pain in primary dysmenorrhea is due to excessive or imbalanced amount of prostaglandins secreted from the endometrium during menstruation. Prostaglandins increase uterine contraction with a dysrhythmic pattern resulting in decreased uterine blood flow and increased peripheral nerve sensitivity which contribute to pain[2]. Treatment is usually with simple analgesics and prostaglandin synthetase inhibitors like Mefenamic Acid 250mg to 500mg three times a day[3]. Treatment should start at the beginning of menstruation and continued regularly during the days affected. In severe cases, the low dose oral contraceptive pill (OCP) can be used. If pain persists in spite of these measures, further evaluation should be initiated to assess for an outflow tract obstruction. MRI or laparoscopy is needed to evaluate congenital anomalies that may cause obstruction and progressive pain in each cycle if the diagnosis is uncertain after physical and Ultrasound examination. Non pharmacological pain management like acupuncture or Transcutaneous Electrical Nerve Stimulation (TENS) may be useful[4].

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Abnormal uterine bleeding in Adolescent

Menstrual cycles that are longer than 42 days or less than 21 days and bleeding that lasts for more than seven days should be considered abnormal particularly after the first two years from the onset of menarche. If the cycle is longer than 90 days even in the first year after menarche, it should be considered as abnormal.

The commonest cause of abnormal uterine bleeding in adolescent is anovulation. In about 95% cases it occurs due to the late maturation of HPO axis with lack of estrogen positive feedback on LH, leading to anovulatory cycle. This results in unopposed action of estrogen on endometrium which eventually breaks down and causes heavy irregular bleeding. The younger the age at menarche, sooner the regular ovulation is established. The possibility of pregnancy must be considered as a cause of abnormal bleeding. Bleeding can be associated with spontaneous abortion, ectopic pregnancy or molar pregnancy. Idiopathic Thrombocytopenic purpura is the most common hematological abnormality

followed by Von Willibrand disease. Other causes include leukemia, hypersplenism, Vit-K deficiency, aspirin and other medication that affect clotting. Endocrine and systemic dysfunction like thyroid dysfunction, hepatic dysfunction and Polycystic Ovarian Syndrome also contribute to the cause of abnormal uterine bleeding in adolescent. Exogenous hormones like Oral Contraceptive Pills (OCP) use is associated with breakthrough bleeding in as many as 30% of individual using OCP. Missing a pill might be also responsible for abnormal bleeding. Sexually active adolescent should be screened for Chlamydia because they have highest rate of Chlamydia infection. Abnormal uterine bleeding can be the initial sign of sexually transmitted infections.

Diagnosis of anovulatory bleeding is by exclusion. A careful general physical examination can reveal signs of androgen excess such as hirsuitism and acanthosis nigricans. A complete pelvic examination should be done in sexually active adolescents. Pregnancy test should be done to exclude pregnancy complications. Adolescents with a history that is classic for anovulation or who deny sexual activity may be managed with limited gynecological examination with pelvic sonography. The initial laboratory tests need not be extensive but must include a hemoglobin estimation, coagulation screen and thyroid function.

Management of bleeding abnormalities related to pregnancy, thyroid dysfunction, hepatic abnormalities, hematologic abnormalities or androgen excess syndromes should be directed to treat the underlying condition. Treatment of anovulatory abnormal bleeding with Mefenamic acid and NSAIDs results in decreased menstrual bleeding compared to placebo[5]. Tranexamic acid is more effective in decreasing heavy menstrual bleeding. Patients need adequate explanations, reassurance and psychological support. Anemia should be corrected by haematinics or blood transfusion in severe cases.

Adolescents with mild abnormal bleeding (adequate Hb% and minimum disruption of daily activities) are best managed with menstrual charting, frequent reassurance, close follow up and supplemental iron therapy. A patient who is mildly anemic will benefit from hormone therapy. Hormone therapy may be prescribed in the form of combined oral contraceptive pills from day 5 to 25 of each cycle, Norethisterone 5 mg three times daily or Medroxyprogesterone acetate 5 to 10 mg daily from day 15 to 25 of each cycle, which help to regulate the cycle and decrease menstrual bleeding.

In cases of moderate to severe bleeding the decision to hospitalize a patient depends on the rate of current bleeding and severity of anemia. After stabilization of the patient, hormonal treatment will control anovulatory bleeding. Combined OCPs 1 to 2 pills twice a day for 5 to 7 days or conjugated estrogen, either 25 to 40 mg given intravenously every 6 hours or 2.5 mg given orally every 6 hours will usually be effective[6]. Oral progesterone therapy should be instituted and continued for several days to stabilize the endometrium. If the hormonal therapy is not effective, the patient should be reevaluated and diagnosis should be reassessed.

Causes of primary amenorrhoea[8]

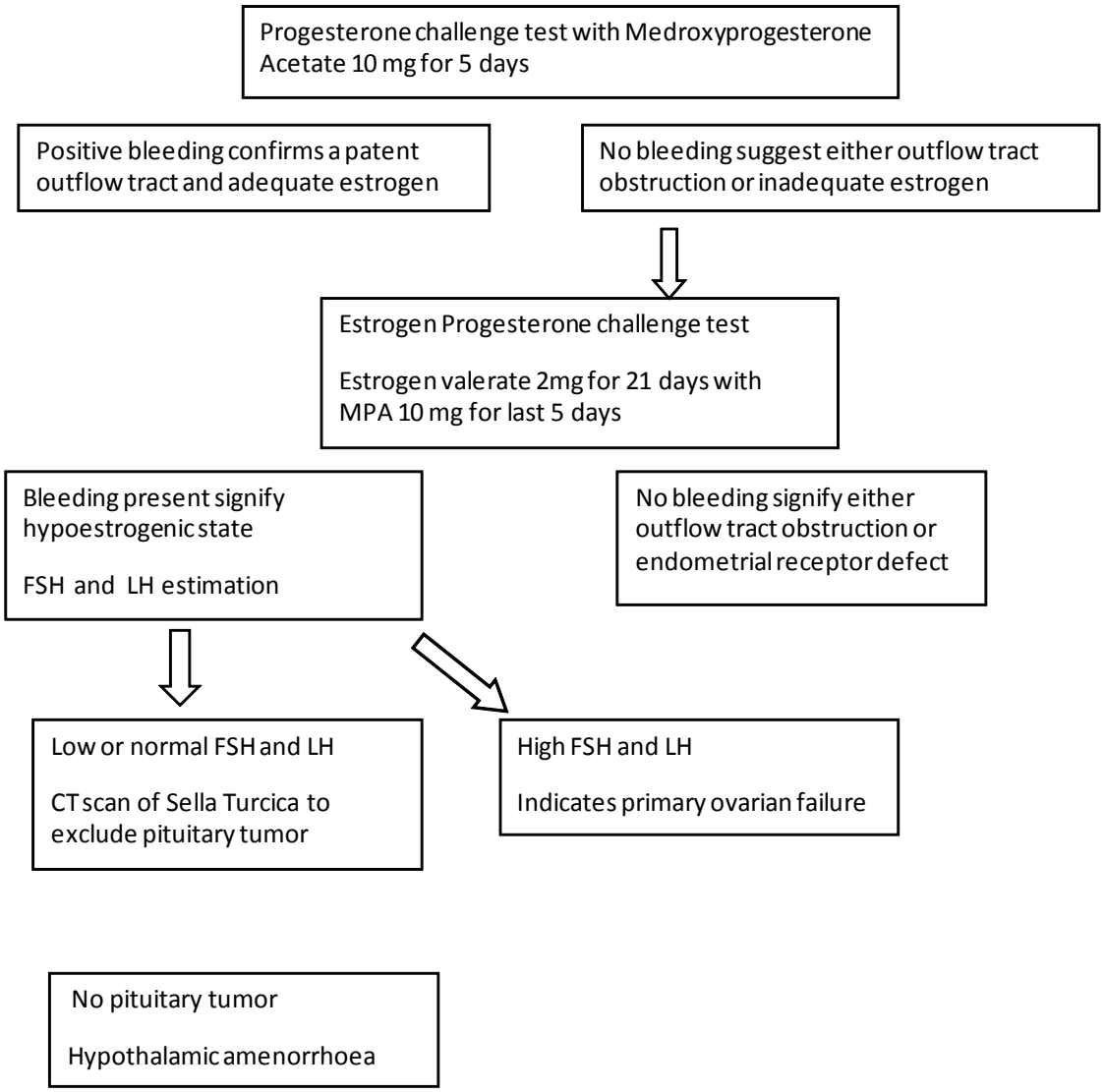
Level I	Extrinsic to the HPO axis	Thyroid and Adrenal disorders Systemic disease Physiological Pregnancy and lactation
Level 2	Hypothalamic	Congenital – Kallman's syndrome Acquired – pituitary stalk disconnection syndrome (craniopharyngioma), excessive weight loss, excessive exercise, cranial radiation
Level 3	Pituitary	Tumours – prolactinomas, nonfunctional tumours Infection – TB Radiation and Surgery
Level 4	Ovarian	Polycystic Ovarian Syndrome Ovarian failure Resistant ovarian syndrome Ovarian agenesis, dysgenesis(Turner's syndrome) Chemotherapy, Radiation, Surgery
Level 5	Utero vaginal	Mullerian agenesis(MRKH syndrome) Testicular feminization, Imperforate hymen Radiation

Amenorrhea

Amenorrhea and oligomenorrhea are condition frequently seen in an outpatient clinic among the young adolescent. Amenorrhea is considered to be primary in a girl who has never menstruated and secondary when there is absence of a period for more than 6 months. Primary amenorrhea is defined as the absence of menses by 13 years of age when there is no visible development of secondary sexual characteristics or by 15 years of age in the presence of normal secondary sexual characteristics[7].

A detailed history should be taken regarding childhood growth and development, family history, cyclical lower abdominal pain, exercise, diet, recent weight change, situations in home and school and psychosocial issue. Symptoms of headache, visual changes, galactorrhoea, virilizing changes and history of trauma, surgery, chemotherapy and radiation should be enquired in details.

Examination of the amenorrheic patient is performed to establish the presence of secondary sexual characteristics and exclude anatomical defect as well as stigmata of chromosomal conditions. Body mass index and signs of virilisation and hirsuitism should be looked for. As most of the patient are young and may not be sexually active, an USG can be a useful alternative to a pelvic examination. The initial investigation should include a baseline blood test for FSH, LH, thyroid function and prolactin. Further investigation then be based on abnormal results and should be directed at the suspected diagnosis. In cases of secondary amenorrhea pregnancy must be excluded.



Management is based on etiology and presence or absence of secondary sexual characteristics. With conditions like gonadal dysgenesis and hypothalamic amenorrhea, treatment is based on hormone replacement given in a way that mimics natural hormone production to induce breast development and withdrawal bleeding and also long term to prevent osteoporosis and cardiovascular disease. Treatment of imperforate hymen is with a cruciate incision of the membrane under general anesthesia. Patient with absent uterus should undergo karyotyping to differentiate between Mullerian agenesis and testicular feminization syndrome. Treatment option for Mullerian agenesis is vaginoplasty after proper counseling and gestational surrogacy. Vaginoplasty with hormone therapy after removal of both the testicles is the treatment of testicular feminization syndrome.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is recognized as the most common endocrinopathy in adolescent presenting with menstrual disorder. In 2003, the Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine (ESHRE/ASRM) – sponsored PCOS consensus workshop group proposed that the diagnosis include two of the following three criteria: oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound; other etiologies of androgen excess must be excluded[9]. The symptoms of PCOS vary with age, race, weight and medication. Adolescent patients pose particular diagnostic problems because characteristics of normal puberty often overlap with signs and symptoms of PCOS. Therefore, different diagnostic criteria for adolescent PCOS have been proposed by some authors. Sultan and Paris recommended that the adolescent girl meet four of the five following criteria: oligo- or amenorrhea 2 years after menarche, clinical hyperandrogenism, biochemical hyperandrogenism, insulin resistance or hyperinsulinemia, and polycystic ovaries on ultrasound[10]. Carmina and colleagues suggested applying the Rotterdam criteria, but limiting definitive diagnosis to the adolescent patient who met all three criteria[11]. These authors suggest that adolescents who exhibit only two of the three criteria may well be diagnosed with PCOS as adults and therefore their symptoms should be followed and reevaluated.

Although the exact etiology of PCOS is unclear, androgen excess is proposed to be a core defect. Increased androgen levels, primarily produced by the ovaries interfere with hypothalamic sensitivity to negative feedback from the ovary, thereby increasing GnRH pulse frequency[12]. This persistently rapid pulse frequency favors increased LH secretion, which in turn stimulates the ovarian theca cells to produce more androgens[13]. The relative decrease in FSH secretion leads to less aromatization of androgens to estradiol and impaired follicular development, resulting in the prolonged periods of oligomenorrhea that are characteristic of PCOS. Hyperinsulinemia is common in healthy adolescents; insulin sensitivity decreases by about 50% and there is a compensatory rise in insulin secretion, which later returns to prepubertal levels in adulthood. However, both insulin resistance and hyperinsulinemia are more severe in adolescents with PCOS compared with the general adolescent population[14]. Insulin stimulates ovarian theca cell synthesis of androgens and inhibits hepatic production of sex hormone–binding globulin. Together, these effects result in increased circulating free androgen levels, thus perpetuating the underlying pathophysiology of PCOS.

Most common clinical feature in adolescent patients with PCOS is menstrual abnormality in the form of oligomenorrhoea, amenorhoea or abnormal uterine bleeding. Patients may present with hyperandrogenic features like hirsutism and acne. Acanthosis nigricans is characterized by specific skin changes due to insulin resistance.

Testing in Adolescents Presenting with PCOS-Like Symptoms:

TSH, Prolactin, Total and free testosterone, dehydro epiandrosterone sulfate (DHEAS), 17-OH progesterone

Ultrasound of ovaries

FSH, LH, estradiol (in amenorrheic adolescents)

Once PCOS has been confirmed

Fasting and 2-hour glucose tolerance test, Lipid profile and Fasting insulin

Adolescent girls diagnosed with PCOS should be informed of the possible long-term risks of type II diabetes, cardiovascular disease, sleep apnea, endometrial carcinoma and psychosocial issues.

The management plan for adolescent PCOS has to be individualized. The first line of treatment for women with PCOS is lifestyle modification including diet, exercise and weight loss. These changes should precede and/or accompany pharmacological treatment. In patient with excess weight, a reduction of as little as 5% of total body weight has been shown to reduce insulin resistance and testosterone levels as well as improving body composition and cardiovascular risk markers[15].

Oligo- or amenorrhea in women with PCOS may predispose to endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with progestogens (Tab. Medroxyprogesterone Acetate 10mg twice daily for 5 days) to induce a withdrawal bleed at least every 3 to 4 months. Oral contraceptive pills can be used for regularization of cycle after proper counseling of the patients and her parents. Patient with hyperandrogenic features may be treated with OCPs containing Cyproterone Acetate or Drosperirone. Excessive hair growth can be treated with waxing, electrolysis, laser and application of Eflornithin hydrochloride topically. Metformin can be considered in patients with PCOS who are already undergoing lifestyle modification and do not have improvement in impaired glucose tolerance and in those women with impaired glucose tolerance.

Adolescence is a dynamic and complex phase of life associated with many different abnormalities that manifest as disorders of menstruation. In order to deal with these problems the gynecologist must maintain a uniform approach to the underlying differential diagnoses. In many a case involving the pediatrician in a shared care might help us more in pinpointing the diagnosis and offering a whole some approach of treatment.

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Announcement

Approach to A Case of Short Stature

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A child's growth pattern is a sensitive indicator of his or her general well being.

Since many centuries, growth monitoring has been an important tool to measure health of Children. Short stature per se is not a diagnosis but a common presenting complaint in Pediatric practice. A systematic approach is helpful to reduce the need for un-necessary and expensive investigations.

Short stature is defined as height below 3rd percentile (more then 2 standard deviations) below the corresponding mean height for a given age, sex and population group. When growth (height) velocity is used, a child is considered 'short' if the child's growth is less than 25th. centile below the mean for that age.

Common Causes of Short Stature – (NO PISCES)

NO - Non-organic i.e psychosocial deprivation.

P - Physiologic

I - Idiopathic or Intrauterine (small for date, TORCH, foetal alcohol syndrome)

S - Skeletal – Skeletal dysplasia, Osteogenesis Imperfecta, spinal defects.

C - Chronic diseases & Chromosomal disorder.

E - Endocrine

S - Social & Psychological.

Physiological Variants Of Short Stature May Be :

(i) Familial

(ii) Constitutional

(iii) Combined familial and constitutional.

Idiopathic short stature is seen in :

(i) Precocious puberty

(ii) Pseudo hypoparathyroidism.

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Chronic disease

(i) Anaemia

(ii) Chronic renal failure

(iii) Congenital heart disease

(vi) Malabsorption syndrome

(v) Chronic lung disease

(vi) Malignancy

(vii) Cystic fibrosis

(viii) Inflammatory bowel disease

Chromosomal

(i) Turner's syndrome (girls specially)

(ii) Down's syndrome

(iii) Prader willi syndrome

Endocrine

(i) Hypothyroidism

(ii) Growth Hormone deficiency (GH)

(iii) Growth hormone insensitivity (Laron syndrome)

(iv) Hypopituitarism

(v) Pseudo hyperparathyroidism

(vi) Cushing's syndrome

(vii) Poorly controlled diabetes.

(A) Important Points In History

1. Antenatal History – We should ask about pregnancy related complications like pre-eclampsia, Gestational, Diabetes, Viral infections, Drug intake in first trimester specially history of maternal smoking or alcohol intake.
2. Birth History – Birth weight, length, gestational age are important to rule out small for date (SFD) Babies.
3. Perinatal complications like hypoglycaemia , convulsions, micropenis (if noted) – May indicate GH deficiency or hypopituitarism. Prolonged physiologic jaundice may

point towards congenital hypothyroidism.

4. *Medical History :*

   Respiratory diseases - Asthma / Congenital heart disease

   Diarrhoea - Coeliac disease / Cystic fibrosis / Malabsorption syndrome/Inflammatory bowel disease.

   Pain in Joints - Juvenile Idiopathic arthritis (JIA) and other rheumatological Conditions.

   Recurrent respiratory – Cystic fibrosis (CF). Nasal polyps, delayed puberty & Infections & diarrhoea failure to thrive may point towards CF.

   History of polyuria/polydipsia / weight Loss / History of headaches / Diabetes / diplopia suggestive of craniopharyngeoma with other pituitary dysfunction. There may be history of recent brain surgery or radiotherapy to brain or spinal cord.

   History of recent weight gain, mood swings and acne – Cushing's syndrome.

   Fatigue / Weight gain / Constipation / dry skin Hypothyroidism.

5. *Family History – Social History :*

   Parental heights to be measured to calculate target height. Weights and heights of siblings to be measured as well.

   History of consanguinity should not be missed

   History of family dynamics can give us a clue to child abuse or neglect. It is a pediatrician's duty to closely observe parent – child interaction.

6. Dietary History :- Detailed assessment of calorie intake and access to food need to be assessed.

7. Drug History : - Chronic use of steroids or any other medicines for any co morbidity to be noted.

8. Developmental History – Development milestones can be delayed in case of Prader willi syndrome, Di George's syndrome, Down's Syndrome, congenital hypothyroidism and in Severe psychosocial deprivation.

(B) Growth measurements

(i) Correct age and sex specific growth chart to be used.

(ii) Length to be measured by infantometer upto 2 years of age and standing height thereafter (on a stadiometer)

(iii) Special charts to be used for syndrome short stature (e.g. Turner's Syndrome, Down's syndrome).

(iv) It is a important to have serial measurements to determine growth velocity. It is calculated as the difference in heights on two different occasions annualized over a year. Growth velocity depends on age and pubertal status.

(v) Body proportion – Upper : Lower segment ratio (U:L) indicates whether Short stature is proportionate (i.e involves the whole body) or disproportionate (involves trunk and arm ones more than the other).

LS Distance between upper border of symphysis pubis and floor in standing Child.

US subtracting LS from standing height

U:L Ratio decreases steadily from birth and reaches a dip during puberty.

U:L Ratio increased – achondroplasia / precocious puberty

U:L Ratio decreased – Skeletal dysplasia involving axial skeleton / spine.

Arm span is approximately equal to height in boys more than 10 years and girls older than 10-14 years. Monitor growth velocity in children with scoliosis, spinal bifida or leg contracture where height can't be used.

(vi) Target height measurement (Mid parental height):

$$\frac{\text{Father's height (in cm.) + mother's height (in cm.)}}{2} \begin{matrix} + 6.5 \text{ (if Male)} \\ - 6.5 \text{ (if Female)} \end{matrix}$$

(vii) Bone age – It is a reliable, cheap and useful tool and a marker of skeletal Maturity. Bone age delay > 2SD i.e more than 2 years is significant. The method used most commonly is that of Greulich and Pyle, which examines epiphysis maturation of hand and wrist.

(viii) Pubertal status needs careful assessment as it indicates skeletal maturation and growth potential. Sexl maturity rating (SMR) is to be regarded in all children with short stature.

(C) Physical Examination

(i) Head to toe examination :

(a) Pallor -> Malignancies/malabsaption syndrome chronic disease

(b) Tachy Cardia -> Heart failure

(c) Brady Cardia -> severe hypothyroidism

(d) Tachypnoea -> Respiratory disorders or congenital heart disease

(e) Midline abnormalities like cleft lip / palate /midfacial hyperplasia, single central incisor -> congenital GH deficiency.

(f) Dry skin / hair loss / coarse fasies -> Hypothyroidism

(g) Blue sclera and fractures -> osteogenesis imperfecta

(h) Bowing of limb or rachitic rosary -> Rickets

(i) Increased weight / buffalo hump / striae / Cushingoid facies -> Cushings syndrome

(j) Cherubic facies (looking younger than age) -> GH deficiency.

(k) Un-explained bruising / caries / poor hygiene / spinal fracture /Severe. Diaper rash -> neglect and child abuse.

(l) Joint swelling -> J I A

(m) Scan to look for spinal and brain surgeries.

(n) Webbed neck / increased carrying angle, wide spaced nipples -> Turner's syndrome.

(ii) Systemic Examination -> pointers

(a) Murmur -> Congenital heart disease

(b) Signs of respiratory diseases -> Tuberculosis, cystic fibrosis, chronic lung Disease.

(c) Abdominal distention -> celiac disease (increasingly reported)

(d) Neurodeficit -> Brain tumors

(D) Laboratory Investigations

Choice of investigations should be guided by good history and examination. The list is as follows :

(i) CBC

(ii) Urea & electrolyte (hypocalcaemia in Digeorge's syndrome)

(iii) E S R

(iv) Tissue transglutaminase

(v) Urine analysis

(vi) Thyroid function test

(vii) Karyotype - Turner's syndrome

(viii) Bone age - X-Ray of wrist

(ix) Insulin like growth factor 1 & IGF binding protein 3 -> GH deficiency (IGF)

(x) GH stimulation tests for GH deficiency

(xi) Diurnal cortisol levels, urinary cortisol levels

(xii) Dexamethasone suppression tests

(xiii) X-Ray wrist & knee & Vitamin D levels for rickets.

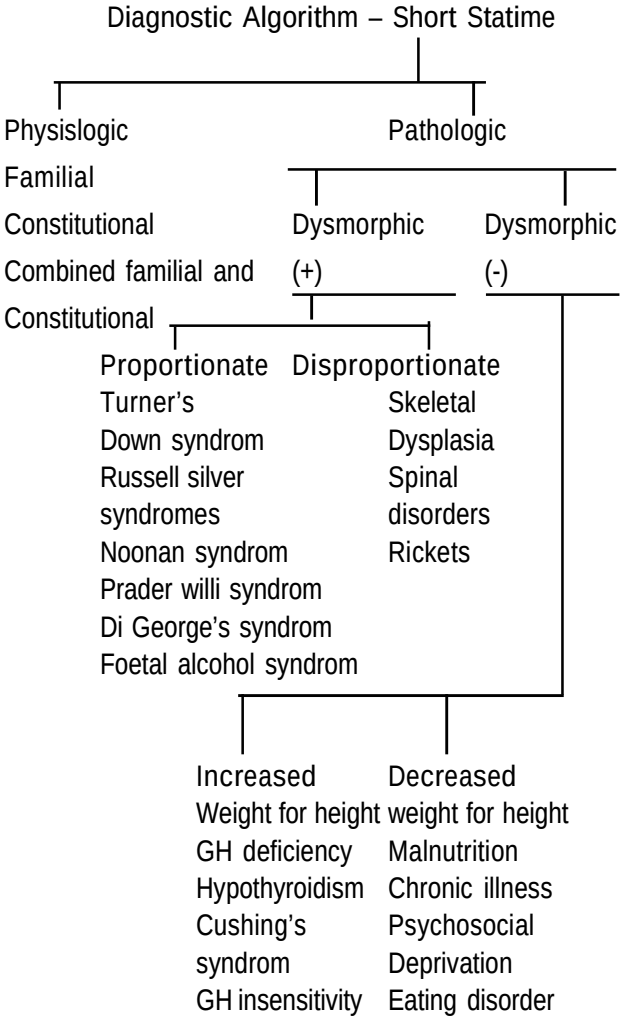
(xiv) Echocardiogram -> For CHD

(xv) Sweat test -> for cystic fibrisis

(xvi) Hb A^1C -> Diabetes

(xvii) Endoscopy -> IBD

(xviii) Referrals to appropriate experts like endocrinologists or psychiatrists for abuse / neglect etc.



Conclusion

Short + Heavy => Endocrine

Short + thin => Systemic disease, PEM

Short with normal velocity -> Constitutional -> delayed bone age, Predicted height appropriate for familial pattern.

(i) Familial (Genetic)

(ii) Bone age = Chronological age

(iii) Normal Velocity

(iv) Predicted height appropriate for familial pattern.

Turner syndrome can have subtle presentation and should not be missed.

Outcome & Treatment -> Depends on etiology.

Familial / constitutional -> Reassurance is enough

Skeletal dysplasia -> May be benefited by limb lengthening procedures.

Specific treatment for chronic diseases

Emotional deprivation is associated with good catch up growth if appropriately addressed.

GH treatment in GH deficiency

Hypothyroidism -> Hormone replacement

Suggested reading

1. Zangar AH, Laway BA, Masoodi SR, et ab. An etiological profile of short stature in the Indian subcontinent. *J Pediatric child health*, 1998, 34 (b) : 571 – 6.
2. A charge SV, Gopal R, Growth hormone disorder : Approach to short stature. *Manual of clinical Endocrinology*, 2015 ; 89a : 777 - 82.
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4. Reiter EO,Rosenfield RG . Normal and aberrant growth.In : Larsa PR, Krokenberg HM , Melmed S, Polonsky KS(eds) .William Textbook of Endocrinology , 12 th edition.Philadelphia: Saunders; 2009; 1003-117

Request

Members are generously requested to provide News, Views, Reviews, Case Reports, Articles to our esteemed journal.

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Answer to Photo Quiz

McCune-Albright syndrome (MAS) consists of at least 2 of the following 3 features:

(1) Polyostotic fibrous dysplasia (PFD),

(2) Café-au-lait skin, and

(3) Autonomous endocrine hyperfunction (eg, gonadotropin-independent precocious puberty). Other endocrine syndromes may be present, including hyperthyroidism, acromegaly, and Cushing syndrome.

Evidence

Arun Manglik

(Dr Arun Kr Manglik, Associate Editor has taken responsibility to apprise us with updates regularly and here are his collection)

Aromatase inhibitors for short stature in male children and adolescents

Background: As a result of the essential role of oestrogens in epiphyseal closure, aromatase inhibitors have been trialled as an intervention to improve height outcomes in male children and adolescents by inhibiting the conversion of testosterone to oestradiol.

Material : We included four RCTs involving 207 participants (84 on interventions) in the review. Trials included males with constitutional delay of growth and puberty (CDGP), idiopathic short stature (ISS), and growth hormone (GH) deficiency.

Conclusion: Available evidence suggested that aromatase inhibitors improved short-term growth outcomes. There was no evidence to support an increase in final adult height, based on limited data, with only one of four trials publishing final height data under non-randomised conditions. Cochrane Systemic reviews DOI: 10.1002/14651858.CD010888.pub2

Surgery for the treatment of obesity in children and adolescents

Background: Child and adolescent overweight and obesity have increased globally, and are associated with significant short and long term health consequences.

Material and Conclusion: l Laparoscopic gastric banding led to greater body weight loss compared to a multi component lifestyle program in one small study with 50 patients. These results do not provide enough data to assess efficacy across populations from different countries, socioeconomic and ethnic backgrounds, who may respond differently. This systematic review highlights the lack of RCTs in this field. Future studies should assess the impact of the surgical procedure and post operative care to minimise adverse events, including the need for post operative adjustments and revisional surgery. Long-term follow-up is also critical to comprehensively assess the impact of surgery as participants enter adulthood. Cochrane Systemic reviews DOI: 10.1002/14651858.CD011740

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Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus

Background: Clinical guidelines differ regarding their recommended blood glucose targets for patients with type 1 diabetes and recent studies on patients with type 2 diabetes suggest that aiming at very low targets can increase the risk of mortality.

Material : We identified 12 trials that fulfilled the inclusion criteria, including a total of 2230 patients.

Conclusion: Tight blood sugar control reduces the risk of developing microvascular diabetes complications. The evidence of benefit is mainly from studies in younger patients at early stages of the disease. Benefits need to be weighed against risks including severe hypoglycaemia, and patient training is an important aspect in practice. The effects of tight blood sugar control seem to become weaker once complications have been manifested. However, further research is needed on this issue. Furthermore, there is a lack of evidence from RCTs on the effects of tight blood sugar control in older patient populations or patients with macrovascular disease. There is no firm evidence for specific blood glucose targets and treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities.

Cochrane Systemic reviews DOI: 10.1002/ 14651858.CD009122.pub2

High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism

Background: Congenital hypothyroidism (CHT) affects approximately one in 3000 to 4000 infants. CHT is one of the most common preventable causes of learning difficulties. Optimal management of CHT requires early diagnosis and prompt treatment to avoid abnormal neurodevelopmental

outcome. One of the main issues in the management of CHT relates to the initial dose of levothyroxine to be used in order to achieve optimal results in terms of intellectual development. Currently, it remains unclear whether high dose thyroid hormone replacement is more effective than low dose in the treatment of CHT. Further research is required to determine an appropriate dose that improves mental and psychomotor developmental outcomes.

Material : The initial search identified 1014 records which identified 13 publications for further examination. After screening the full text of the 13 selected papers, only one study evaluating 47 babies finally met the inclusion criteria. Using the same cohort at two different time periods, the study investigated the effects of high versus low dose thyroid hormone replacement in relation to (1) time taken to achieve euthyroid status and (2) neurodevelopmental outcome.

Conclusion: There is currently only one randomised controlled trial evaluating the effects of high versus low dose of initial thyroid hormone replacement for CHT. There is inadequate evidence to suggest that a high dose is more beneficial compared to a low dose initial thyroid hormone replacement in the treatment of CHT.

Cochrane Systemic reviews DOI: 10.1002/ 14651858.CD006972.pub2

Thyroid hormones for preventing neurodevelopmental impairment in preterm infants

Background: Observational studies have shown an association between transiently low thyroid hormone levels in preterm infants in the first weeks of life (transient hypothyroxinemia) and abnormal neurodevelopmental outcome. Thyroid hormone therapy might prevent this morbidity.

Material : Nine studies were identified that compared thyroid hormone treatment to control. Four randomized (Chowdhry 1984, van Wassenaer 1997; Vanhole 1997; Smith 2000) and one quasi-randomized study (Amato 1989) met inclusion criteria. All studies enrolled preterm infants < 32 weeks gestation, but used different timing, dose and duration of treatment with thyroid hormones. Four studies used thyroxine, whereas Amato 1989 used triiodothyronine. Only two studies with neuro-developmental follow-up were of good methodology (van Wassenaer 1997, Vanhole 1997). All studies were of small size with the largest, van Wassenaer 1997, enrolling 200 infants.

Conclusion: This review does not support the use of thyroid hormones in preterm infants to reduce neonatal mortality, improve neurodevelopmental outcome or to reduce the severity of respiratory distress syndrome. An analyses of data from one study (van Wassenaer 1997) which showed benefits in infants 24-25 weeks gestation was not prespecified and should be treated with caution.

The small number of infants included in trials incorporated in this review limits the power of the meta-analysis to detect clinically important differences in neonatal outcomes.Future trials are warranted and should be of sufficient size to detect clinically important differences in neurodevelopmental outcomes. They should consider enrolling those infants most likely to benefit from thyroid hormone treatment such as infants born at less than 27 weeks gestation.

Cochrane Systemic reviews DOI: 10.1002/ 14651858.CD001070V

Recombinant growth hormone for idiopathic short stature in children and adolescents

Background: Idiopathic short stature (ISS) refers to children who are very short compared with their peers for unknown or hereditary reasons. Recombinant human growth hormone (GH) has been used to increase growth and final height in children with ISS.

Material : Two reviewers assessed studies for inclusion criteria and for methodological quality. Data were extracted by one reviewer and checked by a second. The primary outcome was final height and secondary outcomes included short term growth, health related quality of life and adverse effects. To estimate summary treatment effects, data were pooled, when appropriate using a random effects model.

Conclusion: GH therapy can increase short-term growth and improve (near) final height. Increases in height are such that treated individuals remain relatively short when compared with peers of normal stature. Large, multicentre RCTs are required which should focus on final height and address quality of life and cost issues.

Cochrane Systemic reviews DOI: 10.1002/ 14651858.CD004440.pub2