SOCIETY OF FETAL MEDICINE

Society of Fetal Medicine

SFM Bengal Chronicles

Inaugural Issue

BE AWARE • SHARE • CARE

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From The President's Desk

It's a matter of great pride that having written a number of Honorary Secretary's reports, now I am writing the President's welcome note for our inaugural newsletter! As founder secretary I had the great opportunity of seeing things unfold from inception to this stage for our beloved local chapter.

Bengal Beckons

As we recently got rechristened from SFM Kolkata to SFM Bengal our responsibilities got bigger too. The chapter had a head-start led by two stalwarts like Prof Kamal Oswal and Prof Kusagradhi Ghosh who have raised the bar rather excessively too high for their successors. Now it is upto the new team to carry the rich legacy forward. The job is daunting but highly achievable given the talents we have in the playing 11, officially known as the executive committee members. We also have tremendous potentials in the esteemed members simply waiting to be tapped. It is the bench strength that gives me this level of towering optimism. We have been awarded the best chapter once before and we will do it again.

Be The Change

With your support, the entire group can strive to create a culture of shared learning where every single participant adds value. Your diligent partnerships would help us transform the way our professional development programs are delivered in the days to come. Our membership strength has reached a reasonable strength but it could be even better. Through this newsletter I make my sincere appeal to those who are yet to accept our membership and become a part of the ongoing change in this ever expanding field of medicine. Society of Fetal Medicine brings the global learning opportunities at your doorsteps through focused, high-impact training sessions all round the year. Jump on the academic bandwagon!

The Newsletter

The spirited newly inducted EC members chose to launch this quarterly newsletter in order to enhance communication and share relevant information, the kind of information which may not necessarily be available in the standard medical journals. We will try and keep them theme-based as much as possible. It's a matter of collective pride that we are the first SFM Chapter in the country to introduce its own newsletter. As we unveil the first issue on 8 May 2022, the World Thalassemia Day, the theme couldn't be anything other than Thalassemia! I am grateful to all the respected contributors who readily shared their articles in response to only one simple phone call.

The Pledge

We may not be able to shape your future but we can help you enhance your skills and create a sense of team working. While we wish to bring the best for our unborn children, we also want to support our colleagues in every possible way. Pushing the frontiers of knowledge would be our top priority but we would also have the futuristic approach to keep pace with the recent advances. Finally, this newsletter may appear virtual to you. We may communicate mostly on the virtual platforms. But if you ever need any professional help in these challenging times, please let us know. We live only one phone call away! Never think yourself alone. We are a team. We are a family.

Long live SFM.

Dr. Kanchan Mukherjee
President, Bengal Chapter
Society of Fetal Medicine

Dr. Bimal Sahani
National President, Society of Fetal Medicine

Dear friends,

Everyone is busy. Attention is a precious resource these days. Twitter, which is a prolific social media platform, has brevity at its soul -- just 280 characters. Wisdom lies in being brief but precise.

Jean Baudrillard rightly said, "We live in a world where there is more and more information and less and less meaning." Publishing a scientific newsletter today is therefore both -- a challenge & a necessity.
The challenge is to filter the most, the necessity is to convey the best.

The society of Fetal Medicine is a dynamic organisation. A regular publication that will keep the members abreast with the latest organisational activities and scientific updates goes a long way in being a cohesive force. With this vision, the Bengal chapter of SFM is introducing a quarterly newsletter.

It takes great efforts on the part of the editorial team to ensure the regularity of a publication. It also requires the continued support of members who contribute high-quality content. I am very sure that the West Bengal chapter will do a great job and set a new benchmark in communicating with its members via this newsletter.

On the occasion of World Thalassemia Day today, I would also like to urge our members to create more awareness among our patients about screening for thalassemia and the noble act of blood donation.
My best wishes to the executive body of the Bengal chapter and the editorial team of the Newsletter.

Dr. Bimal Sahani
National President
Society of Fetal Medicine

Prof. Kamal Oswal
Founder President, SFM Kolkata Chapter

I feel honoured and privileged as I write this message for the inaugural issue of our newsletter. There was a time when fetal medicine in this part of the country was being practised almost in isolation. The unmet needs of bridging the gaps was met by Dr Ashok Khurana and his visionary team. It was in Feb 2017 when our journey began from Sagore Dutta Medical College & Hospital with a two-day conference. I was fortunate to have been chosen the founder president. The territory was uncharted but my job was made easy by a spirited team. I couldn't have expected a more supportive executive committee and the members alike.

Continuing medical education was our top priority. Having started with the basics we covered the intermediate and advanced fetal scanning gradually. Learning together from each other has been a different experience altogether. The live demo sessions mostly held at Ramkrishna Mission Seva Pratisthan, Kolkata were made far more interesting by the invited national faculty.

The Society of Fetal Medicine has made major contributions in improving the standards of fetal imaging in the country and West Bengal hasn't remained far behind. The youngsters have come forward alongside the seniors to create an academic bonhomie. Our practice has become multidisciplinary in true senses. Colleagues from different specialities like genetics, paediatric cardiology, paediatric surgery have come forward to make the team even stronger.

I take pride in saying that the local team has developed one of the most vibrant WhatsApp group in the country. Again I must thank the juniors who take the initiatives of creating an atmosphere of learning. The cases posted in our group are of highest standards and help everyone learn at their own comfort.

We started with a membership strength of less than ten. In five years we have just crossed the 100 mark. I think we can do much better on this front too. I urge everyone to take up the membership and enjoy the wide range of benefits.

I am glad the founder secretary Dr Kanchan Mukherjee has taken up the role of President for the state chapter this year. He is supported by an extremely adorable team full of experience and enthusiasm. I am sure they will go a long way in furthering the cause of our beloved society and bring the best possible care for every single mother along with their unborn babies. The newsletter goes a long way in sharing necessary information.
I must congratulate the current executive team for adopting this long term commitment and I wish every success for this newsletter.

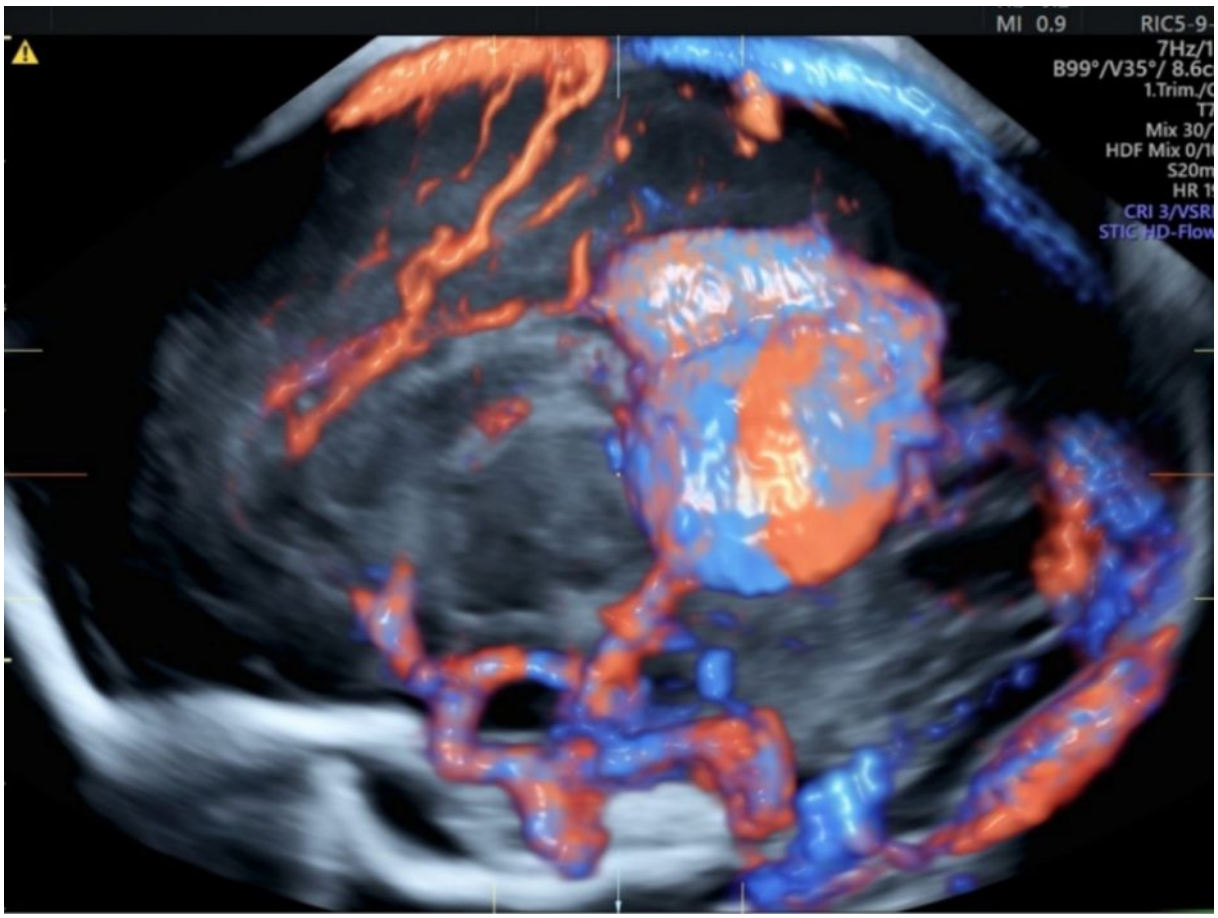
Prof. Kamal Oswal
Founder President
SFM Kolkata Chapter

Quarterly Image Contest
Episode 1

The Bengal Chapter has taken the initiative of holding an image contest for it's members. Only still images were accepted maintaining utmost patient confidentiality. The assessor was blinded to the operator's identities and the scoring was done objectively on various points like resolution of the Image, clinical relevance use of newer technology, legends on the image etc.

In his own words our respected judge Dr TLN Praveen said "Team SFM Bengal, has attempted a very novel method of encouraging the members to excel in imaging and inculcated competetive spirit and in turn exchange knowledge. I really congratulate the whole team for taking up this endeavour and executing it to perfection".

This time we had seven entries and we congratulate Dr Shankar Dey, Ultra Clinic, Asansol for being the winner for this quarter.



The Vein Of Galen Malformation: 3D HD Flow on VCI mode at 32 weeks: Dr Shankar Dey

Prenatal Detection of Thalassemia: Chronicles of three decades

Prof. Kushagradhi Ghosh

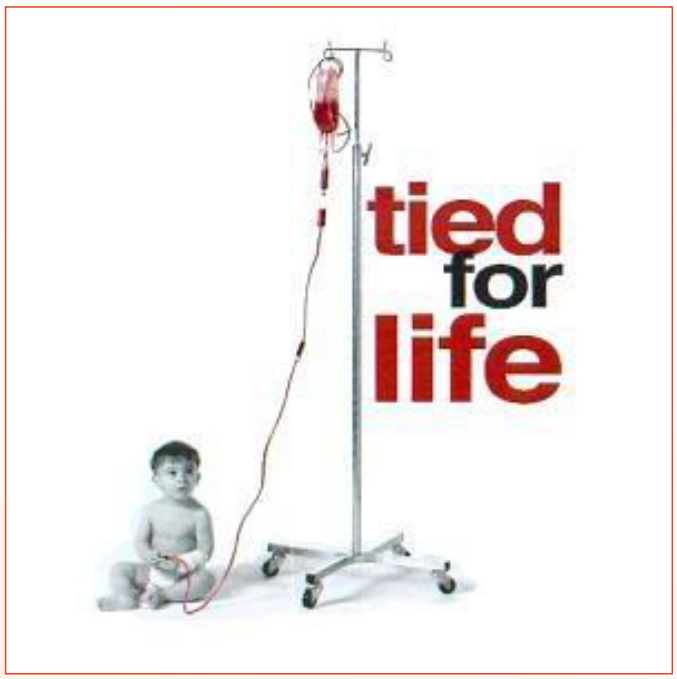
MBBS, MD, DNB, FICOG, FRCOG

RCOG/RCR Postgraduate Diploma in Advanced Fetal USG

'Things change but memories last forever' : Anonymous

As I sit down to pen the thoughts regarding my journey through the crevasses and commissures of prenatal diagnosis of Thalassemia a lot of memories flash through the mind. A young lad lands up in homeland in 1997, full of vigor and enthusiasm, with dream in eyes, daring to peer into the future. The dream was to do 'Fetal Medicine'.

The 'fetus' then, never had the status of a being. As far as babies were concerned, India was grappling with causes of immediate neonatal deaths: prematurity, sepsis, asphyxia, birth trauma and undiagnosed malformations like anencephaly (the commonest anomaly at birth those days!). Prevention of childhood morbidity like thalassemia was at the lowest rung of the ladder.

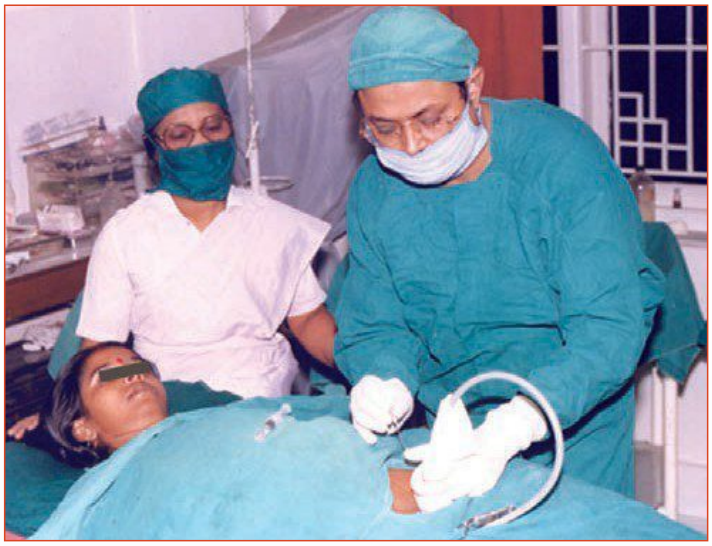


[Pic 1: Tied for Life]

Little do we realize even today that in India more babies are born with thalassemia disease than with down syndrome; and that's the reality.

'The best place to find a helping hand is at the end of your arm': Swedish Proverb

My humble journey in the path of prenatal diagnosis of thalassemia started as a CSIR Pool Officer in OBGYN in my alma mater, Medical College Calcutta. Yours truly is deeply indebted to Dr Mumtaj Sanghamita (then Associate Prof, OBGYN) who encouraged and allowed me to hone my CVS skills on MTP patients.



[Pic 2: CVS Procedure 1999]

I stayed there for six months and moved on to dept of radiology Ramakrishna Mission Seva Pratisthan (RKMSP), Kolkata where I met Dr Kamal Oswal (Lecturer, Radiodiagnosis), one of the nicest person I have ever met. A gynaecologist doing USG was unheard of those days. Yes, you read it right, I was in radio-diagnosis, and did not do OBGYN practice then! I was a misfit, and side by side had to start OBGYN practice again in 1998 for sustenance! At that point of time, the multidisciplinary organization called SFM (started under the leadership of Prof IC Verma, Sir Gangaram Hopsital) was at a very nascent stage. Thanks to the untiring work and leadership ability of Dr Ashok Khurana (who needs no introduction!) that SFM has reached the epitome of national and international force that it is today. We all look after the tiniest of the tiniest patient called the fetus, irrespective of our background; a commendable task indeed. Like everybody else, I feel proud to belong to this family.

'If you want to see the rainbow you got to put up with the rain' : Dolly Parton

The initial days were not so easy. At RKMSP hospital, in 1999, we started routine Hb-Electrophoresis in all antenatal patients in our OBGYN unit. We were astonished looking at our results: a carrier rate of around 5%! But what to do with pregnant patients where both partners were carriers? Fortunately,

there was a PhD research project going on in the dept of biophysics under Prof Uma Dasgupta in Rajabazar Science College, University of Calcutta (it was not Kolkata then). Five mutation analysis was being researched. As luck would have it, we collaborated. They needed clinical samples and we needed mutation analysis. We learnt taking clean samples, moved on from transvaginal to transabdominal CVS, learnt dissecting the villi and transportation. The results were published in 'Prenat Diagn' in 2004. That was the start.

> Prenat Diagn. 2004 Dec 15;24(12):992-6. doi: 10.1002/pd.1049.

Profile of beta-thalassemia in eastern India and its prenatal diagnosis

Aditi Bandyopadhyay [1], Sanmay Bandyopadhyay, Jayasri Basak, Bama Charan Mondal, Anjali Angelika Sarkar, Sunipa Majumdar, Mani Kanchan Das, Sharmila Chandra, Ashis Mukhopadhyay, Mamtaj Sanghamita, Kusagradhi Ghosh, Uma B Dasgupta

Affiliations + expand

PMID: 15614841 DOI: 10.1002/pd.1049

[Pic 3: Title of Publication]

Problems were encountered with high miscarriage rates (2%) maternal cell contamination (2%), missed diagnosis (10%), wrong diagnosis (yes, two such cases!). Fortunately, informed consent for the research protocol saved us, but the faces of the two children and their hapless parents still haunt my memory. Today, a single case of misdiagnosis would be enough to make us pack our bags.

The free research project was over. We had to go commercial. We started collaborating with CMC Vellore, CCMB Hyderabad and Sir Gangaram Hospital. Samples were sent by ordinary cargo flights. There were breakages, bacterial growth in media. Laboratory methods were being perfected (ARMS PCR). There were reports of slow growth, insufficient sample, lack of annealing (which I little understood!). In those days 17 mutation analysis was
performed. The undiagnosed cases were reduced to around 1.8%. We had to counsel patients beforehand that results of CVS might not be available! In some patients who could afford samples were sent to Oxford in UK for rare mutation analysis and reports used to come after a month.

'Always have old memories and new hopes': Arsene Houssaye

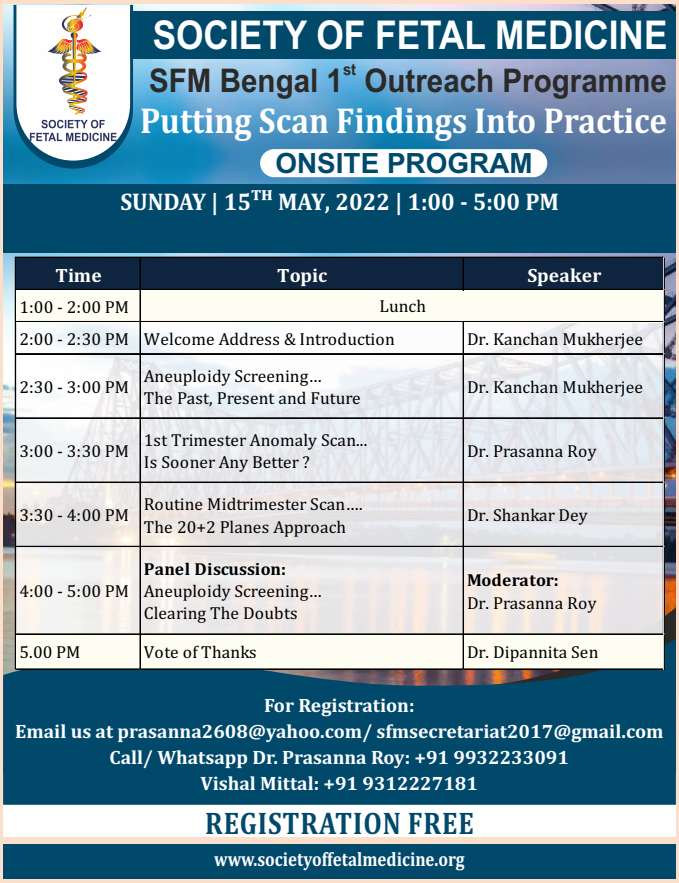
A lot of water has flown under the bridge since then. The whole scenario has changed with the advent of different NGS platforms directly marketed by corporate houses; and the rest is history. These days miscarriage rates, missed diagnosis and wrong diagnosis are close to zero. We hope one day we should be able to diagnose a thalassemic fetus from maternal blood without 'needling' the uterus, and thus avoid a painful existence after birth. And why not hope for a thalassemia free country in near future? Each one of us as champions of fetal health have a responsibility towards it.

[Pic 4: Change of Baton].

As I come to the close of my journey, I earnestly believe the baton would be taken up by the new generation, who are more intelligent, more focused and savvier than us, as is always the case. The last lap of the relay race is yet to dawn.

Outreach CMEs: Your Team Needs You

A huge number of practitioners are working wonders at the periphery. It's high time to interact with them and share each other's wealth of experience. Holding frequent outreach CMEs by a handful few is nearly impossible. Our first peripheral CME is happening on 15 May in Durgapur.



We intend to organise many such outreach activities but that is only possible with YOUR active participation. Members are being requested to come forward and make our team even stronger.

Thalassemia: Failures and Solutions

Dr. Ashok Khurana,
Mentor Emeritus, SFM

On the 8th of May every year, for some time now, we go through a meaningless ritual of rededicating ourselves to "reducing the burden" of Thalassemia. Meaningless, because we have not made any progress worth a mention. We also remind ourselves to improve treatment, and access to treatment, for patients with Thalassemia. We, in India, have come far in the latter consideration, but are sadly far behind the Mediterranean region in the former. Every 10th Thalassemic in the world continues to be an Indian and each year 15000 thalassemics are born. About 42 million carry the B Thal gene and nothing has changed for the better in our national statistics over the past several decades.

Yes, we have a policy in place. The National Health Mission in 2016, issued a Guidelines document on Hemoglobinopathies in India in conjunction with the Ministry of Health and Family Welfare, Government of India, Blood Cell MOHFW and the Rashtriya Bal Swasthya Karyakram.

Yes, we are aware that lack of awareness and consanguinity play a major role in the inability to reduce the number of Thalassemics and that the government and the medical profession have failed to bring about a change.

Most parents, irrespective of personal or religious beliefs, would opt out of a Thalassemic pregnancy, but are not aware of this possibility of a prenatal diagnosis. I do believe though, that all is not lost. It is important to find solutions rather than point fingers at failure.

The efforts to reduce the incidence of disease have been defined and reiterated frequently. The essence of a successful program to reduce the incidence of Thalassemia in the population lies in identifying carrier status. This can be done in an Opportunistic manner, such as in pregnancy, or as newborn screening in a birthing centre, including primary health centres, community health centers, district hospitals, referral hospitals and private hospitals conducted by medical officers, staff nurses, and auxiliary nurse midwives.

It can also be done at a Community level by health teams at Anganwadi centers, government and private schools and colleges. There have been reports from three to four decades ago of such endeavours resulting in a psychologically negative label in the "marriage market" but none such reports in recent times.
Surveys have repeatedly shown that there was insufficient knowledge on the detection of carrier status in children and most of the respondents had not heard of the test for detecting thalassemia carrier status.

The solution is simple: Concerted and repeated efforts at Community Screening, and, re-sensitising Obstetricians and pregnancy healthcare professionals about routine screening for Thalassemia as early in pregnancy as possible.

This, however, needs to be incentive based. A cash bonus for every Thalassemia carrier identified is all that needs to be instituted. In the widespread ambience of commercial gain in today's world, this is perhaps the only answer. The amount that goes into the paid incentive kitty will be a miniscule amount compared to the expenditure of repeated transfusions and heterologous bone arrow transplants.

The second emphasis, especially from the perspective of Fetal Medicine, is the need to evaluate all pregnant women with automated (rather than older methods) red cell counts with confirmation by HPLC analysis for Hb A2 and other hemoglobin variants. The rest of the workup remains the same: partner screening for all couples where a woman is identified to be a carrier, followed by prenatal diagnosis as necessary.

Thirdly, municipal authorities should not issue a marriage certificate unless a Thalassemia screening has been done.

I believe these simple measures are worth a try.

Small gene with big burden: Beta-thalassemia in India

Dr Kausik Mandal, MD (Pediatrics),
DM (Medical Genetics), Additional Professor, SGPGIMS, Lucknow.

Burden of the disease and its distribution in India

Though the burden of genetic disorders is not recognized as worrisome as the infectious diseases in India, this group of disorders is gradually going to be a major public health problem in the coming days. Considering an extremely expanding population, the number of people affected with genetic disorders must have increased exponentially now; an estimation done a decade back had shown that about 495,000 infants with congenital malformations, 390,000 with G6PD deficiency, 21,400 with Down syndrome, 9,000 with β-thalassemia, 5,200 with sickle cell disease (mutation in the same HBB gene causing beta-thalassemia), and 9,760 with amino acid disorders are born every year in India (Verma IC, Bijarnia S. The burden of genetic disorders in India and a framework for community control. 2002).

Hemoglobinopathies arising from mutation in the HBB gene, mainly symptomatic beta-thalassemia and sickle cell disorder, as a group is the most common single gene disorder in India. It is inherited in an autosomal recessive manner, where carriers do not generally manifest the disease but has 25% risk of giving birth to an affected child, when there is chance marriage of two carriers. The frequency of β-thalassemia trait/carrier status has been reported from <1% to 17% and an average of 3–4% throughout India. There is also a regional distribution of the beta-chain-related hemoglobinopathies throughout the country. A high frequency of HbD in the Northern Punjabi population, HbE in the eastern region (West Bengal), and HbS (sickle cell) from populations of tribal origin in central India has been reported. Considering the prevalence of β-thalassemia in India, around 10,000– 12,000 children are born with β-thalassemia major every year.

Understanding nomenclature of mutation in the small gene

HBB gene is a small gene located at 11p15.4. It has got 3 exons (Fig). Like most protein-coding genes, the coding sequence starts with the "ATG" codon which codes for methionine. While giving nomenclature about any sequence change/mutation, the c. number starts from the "A" of "ATG" (e.g. c.20 means 20th nucleotide from the first nucleotide and c.20A > T means at the 20th nucleotide A is replaced by T). The common mutations found in India are c.92 + 5G > C [IVS (IVS stands for intervening sequence) 1-5 G > C], c.92 + 1G > T, and c.92 + 1G > C at splice sites following exon 1; c.51delC, c.26_27insG, and c.92G > C in exon 1; C.126_129delCTTT in exon 2, etc. The old nomenclature used was not standardized and was either using codon number in various ways or using positions in the introns; for example, IVS 1-5 G > C denotes the sequence change in 5th nucleotide in intron 1. Most of the literatures still use the old nomenclature due to its familiarity among physicians and scientists. Previous ARMS-PCR (amplification-refractory mutation system-polymerase chain reaction) was done to look for targeted mutations. Nowadays, Sanger sequencing of coding exons, 5'UTR (untranslated regions, containing the cap site mutations) and conserved splice sites are done to look for all point mutations and small deletions and duplications. There is a common 619bp (base pair) deletion mutation involving the exon 3; for this mutation PCR amplification of two fragments, one amplifying the flanking regions and one amplifying the area of suspected deletion, is being done to detect homozygous or heterozygous mutation.

It is important to note that HbS (sickle cell), HbC, HbD, and HbE (HBB:c.76G > A) are abnormal hemoglobins due to mutation in the beta-chain (HBB gene). Homozygous HbS is SCD and is discussed later. Homozygous HbE has very mild symptoms and may not get detected, except during investigations for any major associated illness. However, HbE along with another pathogenic β0 or β+ mutation is likely to cause thalassemia intermedia, many a times becoming transfusion dependent with time. HbC is a structural variant caused by an amino acid substitution of lysine for glutamic acid at the same codon of HbS (position six after initiation codon) of the beta-hemoglobin chain. Persons with hemoglobin C trait (HbAC) are phenotypically normal. Individuals with hemoglobin C disease (HbCC) may have a mild degree of hemolytic anemia and, splenomegaly. Although the clinical complications of hemoglobin C disease are not very severe, inheritance with other hemoglobinopathies such as hemoglobin S may lead to appreciable consequences. Hemoglobin D carriers (HbAD) and homozygous HbD disease (HbDD) have no or mild phenotypes, and at times remain nonrecognizable even when they co-occur with another beta-mutation. HbD can be due to various mutations; HbD Punjab is a very specific mutation in exon 3. Otherwise, exon 3 mutations are very rare.

Manifestations of the disease:

β-thalassemia as per severity of disease is divided into:

Thalassemia major

Thalassemia intermedia

Thalassemia minor (Carriers with mutation in one allele)

RBC indices and Hb variant by HPLC (High-performance liquid chromatography) is the key to the diagnosis of beta-thalassemia and carrier detection:

RBC indices for diagnosis of beta-thalassemia

Data from Galanello et al [1979]

	Normal	Normal	Affected	Carrier
	Male	Female	β-Thal Major	β-Thal Minor
Mean corpuscular volume (MCV fl)	89.1±5.01	87.6±5.5	50-70	<79
Mean corpuscular hemoglobin (MCH pg)	30.9±1.9	30.2±2.1	12-20	<27
Hemoglobin (Hb g/dL)	15.9±1.0	14.0±0.9	<7	Males: 11.5-15.3 Females: 9.1-14

HPLC for Hb Variant for diagnosis of beta-thalassemia after 1 year of age

Data from Telen & Kaufman [1999]

	Normal	Affected (thalassemia major or intermedia)		Thalassemia minor/ Carrier
		* β^0/β^0	# β^+/β^+ or β^0/β^+	
HbA	96%-98%	0	10%-30%	92%-95%
HbF	<1%	95%-98%	70%-90%	0.5%-4%
HbA_2	2%-3%	2%-5%	2%-5%	>3.5%

Genetic Counseling and Prenatal Testing

Beta-thalassemia is an autosomal recessive genetic disorder. The parents of an affected child are asymptomatic carriers. When parents are carriers, the risk of having an affected child is 25%. Carrier testing by RBC indices and Hb variant by HPLC is indicated in all couples from southeast Asia, especially in communities where the disease is prevalent and in at-risk family members of an affected child. When both the spouses are found to be carriers, mutation testing is indicated to identify the putative mutations. Prenatal testing during pregnancy is being offered to know the status of the baby. When there is an affected child with homozygous or compound heterozygous mutations, prenatal testing is being provided in every subsequent pregnancy. Prenatal testing is done from DNA extracted from samples obtained by CVS (chorionic villous sampling) in earlier weeks (around 12 weeks) or amniocentesis in later part (16–20 weeks) of pregnancy. CVS is preferred, since it provides better DNA and has an advantage of earlier detection. It is important to note that detection of mutation in the proband or the carrier parents is essential before offering prenatal testing.

Figure:

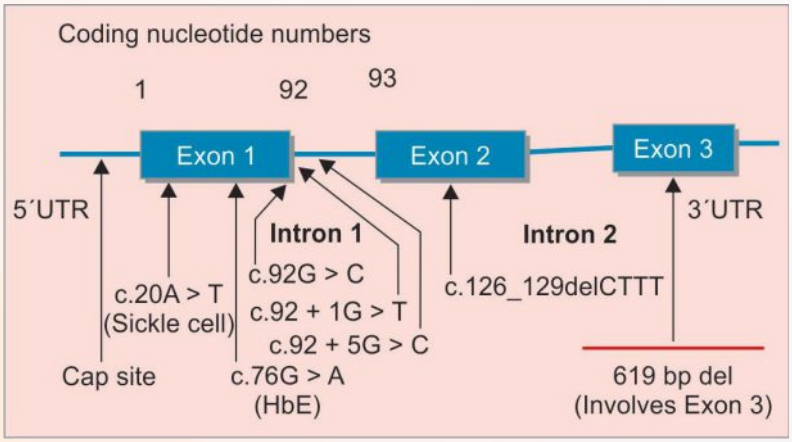


Figure legend: HBB gene: It contains 3 exons. The various common mutations and their positions are marked. The most common mutation, c.92 + 5G > C is located in intron 1, 5 nucleotide downstream of the last nucleotide (c.92) of exon 1. The 619bp deletion involves exon 3.

Table of genetic risks

The main genetic risks for couples with a haemoglobinopathy that can result in an affected pregnancy are summarised in the table below (courtesy of Prof. B. Modell):

Carrier of:	α^+ thal	α^0 thal	Hb S	β thal	δβ thal	Hb Lepore	Hb E	Hb O Arab	Hb C	Hb D Punjab	Hb Lepore	Not a carrier
α^+ thal												
α^0 thal												
Hb S												
β thal												
δβ thal												
Hb Lepore												
Hb E												
Hb O Arab												
Hb C												
Hb D Punjab												
HPFH												
Not a carrier												

Key:

	Serious risk
	Less serious risk
	Possible hidden risk
	No risk

We thank our esteemed authors who despite their busy schedules spent valuable time to write for our newsletter.

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