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**Chettinad**  
Health City

# Chettinad Health City

## MEDICAL JOURNAL

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- Impact of Mobile Phone Radiation on Ejaculated Semen
- Influence of Sperm Parameters on IUI Success
- Leucocytospermia – Does it Mean Anything?
- Lifestyle and Environmental Factors Influencing Male Fertility
- Undescended Testis
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- Pages of History – Deliverance of One Genius by Another
- Dialogue with the Stalwart – Dr.B.N.Chakravarty



# TB UNMASKED

Healthcare workers on the front lines of the tuberculosis epidemic

## Healthcare Workers are Dying to Help

Healthcare workers risk getting TB at much higher rates than the general population:

2x

United States

5x

South Africa

5-11x

India

12x

Thailand

Patient contact is the main factor putting healthcare workers at risk.

Up to 80% of TB cases among healthcare workers can be connected to their work.

On average 1 person with active TB can spread it to 10-15 people in a year.



In 2014, in Texas a healthcare worker exposed approximately 860 babies and 43 fellow healthcare workers to TB.



## TB Prevention Saves Lives and Money

Drug-resistant TB is more expensive and more deadly. In the United States, the cost to treat one patient:

\$134,000

MDR-TB

\$483,000

XDR-TB

Global spending on new TB vaccine development is just 25% of what's needed, part of a \$1.3 billion overall funding gap in 2013.

Healthcare workers deserve the investment in their protection

## It Doesn't Have To Be This Way

Those who are dedicated to caring for others deserve to be protected from TB. Healthcare workers are catalysts for change.

Short term solutions:

Administrative controls (early identification and patient management), improved training and education, infection control measures, policy changes, increased TB awareness and education, commitment to R&D for new tools to fight TB

Long-term solution:

## CREATION OF AN EFFECTIVE TB VACCINE

## The Global TB Crisis

In 2013, there were

9,000,000  
new TB cases

&

1,500,000  
deaths

1 death every 21 seconds

Healthcare workers around the world are at risk of TB and they deserve to be protected.

## Ways to Stay Safe

Early patient identification and management

Rapid diagnosis and treatment

Germicidal lights

N95 masks - availability and training on proper use

Improved ventilation

Improved infection control measures

Increased training and awareness

Get involved! Learn more at [tbusmasked.org](http://tbusmasked.org)

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## Editorial

It is my pleasure to meet all of you through this issue of the journal.

The whole universe spins on an invisible balance between two forces. The continuation of the human race is not an exception to this rule. The contribution from male and female is essential for a healthy progeny. Though the females are commonly blamed for infertility, it is a fact that male factors are equally contributory. The original and review articles in this issue focus on male factor ranging from congenital factors to environmental factors.

Mobile phones have become ubiquitous and the article on impact of mobile phones on the ejaculated sperm parameters highlights the harm it may pose to male fertility. The article on impact of life style and environmental factors on semen parameters further expands ones knowledge on the importance of life style modification and creating awareness regarding the avoidable factors in male infertility. While the article on leucocytospermia reassures us about the lack of correlation between the presence of leucocytes in semen and infective pathology, the one on undescended testes hypothesizes on the possibility of an abnormally developed testes causing its own maldescent. The original article on the predictive capacity of the sperm parameters in IUI success reiterates how implementing WHO 2010 criteria for morphology can actually help in decision making regarding treating patients with IUI or ICSI.

There is an array of interesting case reports which highlights the importance of being alert, high in clinical acumen and the need to keep other disciplines in the loop while dealing with uncommon situations.

It befits this journal issue focusing on infertility to include the history of evolution of Assisted Reproductive Technology in India and the personalities who shaped up this history. The history makes us feel proud as Indians, considering the remarkable achievements made by Dr.Subash Mukerjee and Dr.T.C.Anand Kumar. Let us salute them.

In the "Dialogue with the stalwart " section– Prof.B.N. Chakravarty delves in to the depths of infertility and also defines the quality of a best teacher.

News and views is a new addition and this month's issue deals with the promise of vaccinology which is an unbiased opinion on existing practical need for further research in this field and the need for universal coverage. Interesting Medical updates complete the issue.

Relish the feast of knowledge and give us your feedback so that we can improve further.

**Dr. Kanchana Devi B**

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## Original Article

# Impact of Radiation Emitted by Mobile Phone During Call Mode on the Ejaculated Semen

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### Abstract

**Objective:** To study the motility changes in the human spermatozoa after exposure to Radio Frequency Electromagnetic Waves (RF-EMWs) emitted by the cell phone during the call attended mode from different directions.

**Design:** Prospective single blind study.

**Settings:** Central Animal facility, Department of Reproductive Medicine, Chettinad Super Speciality Hospital.

**Patients:** Thirty men with normozoospermia were randomly selected from those attending the infertility clinic were randomly selected, during the months of January to May 2013.

**Interventions:** The semen samples were collected soon after ejaculation and sperm concentration and motility were assessed and noted. Then the sample was taken to the animal facility for the RF-EMWs exposure for 1 hour and then again the sperm concentration and motility was evaluated and noted.

**Results :** Exposure of the semen sample to the RF-EMWs produces a negative effect on the sperm motility. There is a statistically significant decline in the sperm motility after RF-EMW exposure for one hour.

**Conclusion :** After RF-EMWs exposure there is a definitive decline in the sperm motility when compared to the control group.

**Key Words:** RF-EMWs, Spermatozoa motility, Mobile phone

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### Introduction

Male reproduction is partly affected due to the innovations in cell phones which also have detrimental effects on the human brain and cardiovascular system<sup>1</sup>. In the last decade there has been a tremendous development and use of mobile telecommunication services which drastically increased the amount of radiofrequency electromagnetic wave (RF-EMW) exposure in daily use; this has harmful effects on human health. In 1996 the World Health Organization (WHO) established the International EMF Project to assess the scientific evidence of possible health effects in the range of 30 Hz to 300 GHz of electromagnetic frequencies<sup>2</sup>.

These phones operate at different frequencies in different countries and continents, differing in respect to the frequency usage. Cell phone companies have assured people for years that cell phones are safe. However, literature reports of adverse effects of RF EMW emitted from cell phones on biological systems is available. Recent studies on EMW emitted from cell phones suggest that they can reduce the fertilizing potential of men<sup>3-7</sup>. Specific absorption rate (SAR) is a measure of the rate at which energy is absorbed by the body when exposed to a radio frequency (RF)

electromagnetic field. It is the power absorbed per mass of tissue and is expressed in units of watts per kilogram (W/kg)<sup>8</sup>. It is generally recognized that most of the men place the mobile phones in their trouser pockets, adjacent to the testis. Thereby, a possibility exists that the testicular tissue is constantly exposed to RF-EMWs.

In our study, we strived to determine whether the RF EMWs emitted from the cell phone in talk mode (call attended mode) from different directions may negatively affect sperms and impair male fertility.

### Methodology

**Type of Research Study:** A prospective single blinded study conducted at the Central Animal facility, Department of Reproductive Medicine, Chettinad Super Speciality Hospital.

The study involved thirty healthy men with normozoospermia who were selected randomly from those attending the infertility clinic in the department of Reproductive Medicine, Chettinad Super Speciality Hospital from January to May 2013. They were in the age group of 25 to 48 years, with abstinence from sexual activity ranging between 2 to 14 days. Semen

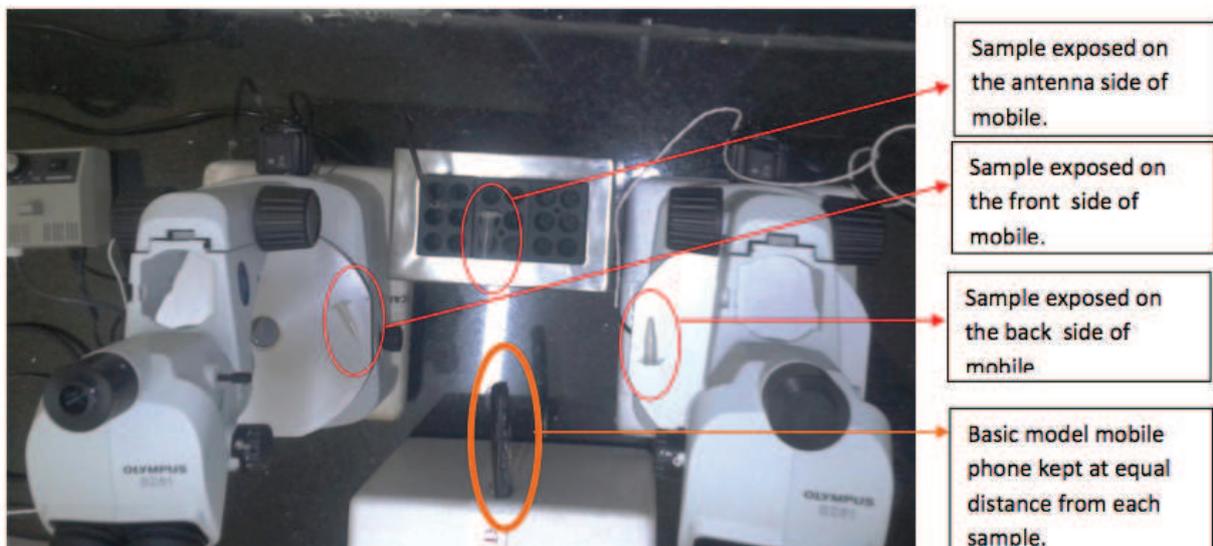
samples with volume more than 1.5 ml were included (Table 1). Written and informed consent was obtained from each participant in their own vernacular language and in English. IRB approval was not obtained because only the semen samples that were to be discarded after the semen analysis were included in the study.

The participants were requested to collect the semen sample in a clean non toxic container by masturbation. The samples were kept at 37° C for liquefaction before analysis. Upon liquefaction, semen analysis was done as per the WHO criteria 2010.

After the primary analysis, the remaining semen sample was homogenized and aliquoted into 4 different vials

generated power density of 16.53 minimum and 233.67 maximum with an average of 63.57 in the front side of the mobile, then the power density at the back was 15.26 minimum and 270.86 maximum with an average of 70.5, at the antenna side the power density was 23.97 minimum and 302.67 maximum with an average of 103.5 (Table 2). These power density measurements were taken with the help of a field strength meter (Fig 2) by the research scholars of Dept. of Electronics and Communication, Anna University, Guindy College of Engineering, Chennai.

According to the International Commission for Non-ionizing Radiation Protection (ICNIRP 1998) and the Federal Communications Commission (FCC 1999),



**Fig 1:** View of the setup from the top

and were taken to the animal facility for RF EMWs exposure.

### RF-EMWs exposure

A basic model mobile phone was taken for the RF EMWs exposure with 90% of battery point and at the place where there was at least 4 points signal (tower availability). Then the sample in the 4 vials were kept at 4 different places, one in the incubator which serves as the control, one in front of the mobile, one at the back and one at the antenna side each at a distance of 2.5 cm away from the mobile. The samples which were placed at the front, back and antenna side were placed on a warm stage so that there was no effect in the sperm motility due to temperature variations (Fig 1).

Then the mobile was activated in a call attended mode with another mobile away from the research field for an hour. During the call attended mode the mobile

the reference level for exposure of RF-EMWs is peak power density<sup>9</sup>.

### Post RF-EMWs exposure analysis

After one hour, the four aliquots were re-analyzed for the sperm concentration and the motility estimation was done by placing 5 µl of the well mixed post RF EMWs exposed samples from the front, back and antenna sides and control sample (incubator) was placed on a glass slide covered with cover slip under 40 x magnification. Totally 100 spermatozoa were graded into progressively motile (PR), non progressively motile (NP) and immotile (IM). Each value was noted separately and analyzed later. The whole study was conducted by the same observer and the analyst of the sample after exposure was blinded to the sample analyzed. The data were analyzed using SPSS software. P-values were calculated using paired t -test.

**Table 1:** Descriptive analysis of participants and samples of the study (N=30)

Parameter	Mean	Std deviation	Minimum	Maximum
Age in years	32	4.9	25	48
Volume of semen collected in ml	3.03	1.51	1.5	8
pH of the semen	8.1	0.35	7.5	9.5
Abstinence in days			2	14

**Table 2:** Power density generated by the mobile in the call attended mode at different places

Power density generated	Front	Back	Antenna
Minimum	16.53	15.26	23.97
Maximum	233.67	270.86	302.67
Average	63.57	70.5	103.5

**Fig 2:** Field strength meter used to measure the power density.

Compared to the control group, there was 7.6% decline in mean percentage of progressively motile sperms in the group exposed from the back of the mobile, which is statistically significant (95% CI -11.74 to -3.45, p value 0.001). There was a slight decline of 0.83% in the mean percentage of non progressive sperms. The mean percentage of immotile sperms had increased by 8.4%, which was statistically significant (95% CI 4.48 to 12.31, p value 0.00). (Table 4)

Compared to the control group, there was 12.23% decline in mean percentage of progressively motile sperms in the group exposed from the antenna of the mobile, which was statistically significant (95% CI -16.46 to -8.00, p value 0.00). There was a decline of 2.33% in the mean percentage of non progressive sperms. The mean percentage of immotile sperms had increased 14.56%, which was statistically significant (95% CI 9.14 to 19.98, p value 0.00). The mean percentage difference among different sides of the antenna are given in table 5.

**Table 3:** Comparison of quality of sperms between control group Vs exposed group from behind (N=30)

Quality of sperms	Mean % Exposed from back	Mean % control	Mean % difference	95%CI		P-value (Paired t test)
				Lower	Upper	
Progressively motile	25.03%	32.63%	-7.60%	-11.74%	-3.45%	0.001
Motile- Non progressive	22.23%	23.06%	-0.83%	-4.75%	3.09%	0.66
Immotile	52.73%	44.33%	8.40%	4.48%	12.31%	0.000

**Table 4:** Comparison of quality of sperms between control group Vs exposed group from Antenna (N=30)

Quality of sperms	Mean % Exposed from antenna	Mean % control	Mean % difference	95%CI		P-value (Paired t test)
				Lower	Upper	
Progressively motile	20.40	32.63%	-12.23%	-16.46%	-8.00%	0.000
Motile- Non progressive	20.73	23.06%	-2.33%	-5.31%	0.64%	0.12
Immotile	58.90	44.33%	14.56%	9.14%	19.98%	0.000

**Table 5:** Mean % Difference Comparison between Front, Back & Antenna side

Quality of sperms	Mean% Difference of front exposure group	Mean% Difference of back exposure group	Mean% Difference of antenna exposure group
PM	-4.26%	-7.60%	-12.23%
NPM	0.46%	0.83%	-2.33%
IM	3.76%	8.40%	14.56%

## Results

Compared to the control group, there was 4.26% decline in mean percentage of progressively motile sperms in the group exposed from the front side of the mobile, which is statistically significant (95% CI -8.18% to -0.34%, p value 0.03). There was a slight increase of 0.46% in the mean percentage of non progressive sperms. The mean percentage of immotile sperms had increased to 3.76%, which was statistically significant (95% CI 0.77% to 6.76%, p value 0.01). (Table 3)

## Discussion

According to a study in 2006, significant decrease in sperm motility was observed after exposure to EMR. Results between the control and the EMR exposure group showed statistically significant changes in sperm motility<sup>6</sup>.

In 2009, De luliis G.N et al., conducted a study on purified human spermatozoa exposed to RF-EMR. Motility and vitality were significantly reduced when SAR was increased. The DNA fragmentation and generation of ROS (reactive oxygen species) were significantly elevated (p <0.001). Therefore, these findings show that use of mobile phones potentially affects the health, fertility and wellbeing of their offspring in the reproductive age group men<sup>10</sup>.

A study by Agarwal A et al in the year 2008<sup>7</sup>, compared the semen parameters with different cell phone usages. Totally 361 men were divided into four groups according to their active cell phone use: group A: no use; group B: <2 h/day; group C: 2-4 h/day; and group D: >4 h/day. The comparisons of semen

parameters between these groups were statistically significant. As the duration of daily exposure to cell phones increased, the sperm parameters decreased. Therefore, the author concluded that, decrease in sperm parameters was dependent on the duration of daily exposure to cell phones. The same author in 2009, extended his study to normal healthy donors ( $n=23$ ) and infertile patients ( $n = 9$ ). The objective was to evaluate unprocessed (neat) ejaculated human semen after radiofrequency electromagnetic waves (RF-EMW) exposure from mobile phone during talk mode. Neat samples were divided into 2 aliquots after liquefaction. One aliquot was exposed to cellular phone radiation (in talk mode) for 1 h, and the second aliquot served as the control. Results showed samples exposed to RF-EMW had a significant decrease in sperm motility and viability. Levels of DNA damage showed no significant difference<sup>11</sup>.

In a study by Nadia Falzone et al<sup>12</sup>, they examined the effect of 900 MHz GSM radiation on the induction of pro-apoptosis events such as activity of caspases, externalization of phosphatidylserine, DNA strand breaks and activation of ROS in human spermatozoa. The study concluded no evidence of any in vitro effect of RF EMF exposure on caspase activation, DNA fragmentation, phosphatidylserine expression (pro-apoptosis) or ROS generation in human spermatozoa. These results appear to be reliable because great care was taken to rule out any temperature rise related effects.

Available scientific evidence shows mobile phone usage decreases semen quality. One study suggests that semen quality is influenced by lifestyle and that use of mobile phones close to the testes can decrease semen quality<sup>5</sup>. Another study suggests pro-longed use affects sperm motility characteristics<sup>4</sup>.

DNA damage (spermatogenesis and sperm maturation level) results from cellular phone EMR<sup>13</sup>. DNA damage in sperm cells by RF radiation exposure, has been shown to affect sperm motility<sup>3,4,6</sup> and a negative correlation exists between sperm chromatin damage and sperm motility<sup>14</sup>.

According to our results there is a statistically significant decline in percentage of progressively motile sperms in all the exposure groups compared to the control group. Therefore the RF EMWs have a significant impairment on the sperm motility irrespective of the side of exposure from the mobile phone. Therefore we suggest that placing of mobile phones during call attended mode in the trouser pockets, while using hands-free or bluetooth devices, would definitely impair male fertility.

## Conclusion

Awareness regarding the potential hazards of the cell phone usage on the man's fertility has to be created among the public. Measures have to be taken to reduce the use of this modern gadget to the barest minimum possible by all age group of men and women to avoid health risks and especially to reproduction.

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We thank Mr.S.Ramprabhu, PG Scholar, Microwave Laboratory, Department of ECE, Anna University, Chennai, who took the measurement using the Field Strength Meter.

The authors declare no conflict of interest.

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### **Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)**

Majority of studies have rarely observed clear dose-response relationships between intakes of vitamin D, alone or in combination with calcium, and health outcomes. Although a large number of new studies (and longer follow-ups to older studies) were identified, particularly for cardiovascular outcomes, all-cause mortality, several types of cancer, and intermediate outcomes for bone health, no firm conclusions have been drawn so far. Studies suggest a possible U-shaped association between serum 25(OH)D concentrations and both all-cause mortality and hypertension and also suggest that the level of supplemental vitamin D and calcium administered in the Women's Health Initiative Calcium-Vitamin D Trial are not associated with an increased risk for cardiovascular disease or cancer among postmenopausal women who are not taking additional supplemental vitamin D and calcium. Studies suggest the method used to assay 25(OH)D may influence the outcomes of dose-response assessments. Beyond these observations, it is difficult to make any substantive statements on the basis of the available evidence concerning the association of either serum 25(OH)D concentration, vitamin D supplementation, calcium intake, or the combination of both nutrients, with the various health outcomes because most of the findings were inconsistent. [Agency for Healthcare Research and Quality \(US\): 2014 Sep.](#)

**- Prof. RM. Pitchappan**

# Original Article

## Prognostic Value of Different Sperm Parameters on the Success of Intrauterine Insemination

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### Abstract

**Objective:** To identify the sperm parameters which influence the success of an Intra uterine insemination (IUI) cycle. Design: A retrospective study conducted at the Dept. of Reproductive Medicine, Chettinad Super Specialty hospital, Chennai.

**Patients:** Study includes 518 IUI cycles from April 2011 to December 2013.

**Methodology:** Ovarian stimulation was done with clomiphene citrate alone or in combination with gonadotrophins, depending on the patient's response. In majority of the patients HCG was administered as a trigger. Semen samples were analyzed according to WHO 2010 standards and processed by either direct swim up, pellet with swim up or density gradient methods, according to the nature of the sample.

**Results:** The overall pregnancy rate was 13.5%. When all the 3 sperm parameters (concentration, motility, morphology) were taken into consideration, variable sperm concentrations did not have a significant impact on the pregnancy rate when it was above 1mil/ml. There was no statistically significant difference in the pregnancy rates among the two motility groups (<32% and ≥32% pre-wash progressive motility) but normal sperm morphology (≥4%, WHO 2010 criteria) showed high prognostic value (p 0.024).

**Key Words:** Sperm parameters, IUI, Prognostic value, Success rate

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### Introduction

Artificial insemination dates back to early 1900's when neat semen was injected into the reproductive tract of a female in order to achieve a pregnancy<sup>1</sup>. Now with advancements in the field of reproductive medicine, artificial insemination has taken a more refined name of intra uterine insemination (IUI) involving preparation of semen sample and ovarian stimulation.

IUI is a simple, relatively less-invasive and less-expensive mode of Assisted Reproduction technology (ART) treatment given before advancing towards more complex and expensive procedures like In vitro fertilization (IVF) or Intra cytoplasmic sperm injection (ICSI). It is widely used to treat couples with different etiologies including coital problems, anovulation, idiopathic and also mild to moderate male factor issues<sup>2</sup>. However, the pregnancy rates, across the world differ with each variable in an IUI cycle. This could be because most studies while not only being retrospective, also have different study groups, varied stimulation protocols, the number of inseminations, method of semen processing etc<sup>3</sup>.

There are multiple factors which influence the outcome of an IUI viz., age of the patient, duration and type of infertility and stimulation protocols<sup>2</sup> and patients' follicular response and of course, the sperm

parameters. There have been multiple studies stating sperm morphology, motility and total motile sperm count (TMSC) are of predictive value in an IUI cycle<sup>2-5</sup>. However, it still remains unproven as to which among all the sperm parameters is the most essential for pregnancy, making it difficult to define the "ideal sperm quality". Therefore, to restrict patients for IUI treatment based on their semen quality seems unjustified.

This retrospective study aims to evaluate the different sperm parameters and their prognostic value in an IUI cycle.

### Materials and methods

This retrospective study was conducted at the Dept. of Reproductive Medicine, Chettinad Hospital & Research Institute, Chennai. The study included 518 infertile couples posted for IUI treatment from April 2011 to December 2013. The general characteristics of the patients are described in Table 1 and the prewash sperm parameters in Table 2.

Ovarian stimulation was done with clomiphene citrate alone or along with FSH or HMG, the duration and dosage depending on the patients' response. For clomiphene citrate-stimulated cycles, 50-100 mg clomiphene citrate was given on days 2-6 and when

combined with FSH/HMG the gonadotrophins were administered at 75-150 IU either on alternate days or daily. Transvaginal ultrasound scan was done to determine the number of follicles, mean follicular diameter and thickness of the endometrium. When at least one or two follicles measured 17 mm or more and endometrial thickness of >8mm, 5000 IU hCG injection was administered as trigger 40h after which IUI was done. For patients with multiple follicles GnRH analogue was given as trigger.

**Table 1:** Demographic pattern

General Parameters	Median
Age of Husband(yrs)	34
Age of wife(yrs)	29.5
Duration of Infertility(yrs)	4.75
Endometrial thickness(mm)	9.65

**Table 2:** Pre-wash sperm parameters

Sperm parameters	Median
Sperm concentration (mil/ml)	49.5
Progressive motility(%)	34.5
Morphology(%)	11

**Table 3:** Indications for infertility

Indications	Distribution (%)	Pregnancy (%)
Anovulation	37.6	16.4
Anovulation+ single patent tube	1.2	0
Single patent tube	5.6	13.8
Endometriosis	1.9	0
Congenital Uterine anomalies	1.4	0
Male factor	8.3	14
Combined causes (male and female)	2.3	0
Unexplained	41.7	13

**Semen processing:** On the day of IUI, semen samples were subjected to analysis according to the WHO criteria, 2010<sup>6</sup>. The samples were then processed either by swim-up method or pellet with swim up method or discontinuous double density gradient techniques, depending on the nature of the sample. The media used for sperm processing were Quinn's advantage sperm washing media and Quinn's double density gradient media (40% & 80%). The swim up method and double density gradient method are as detailed in the WHO manual, 2010<sup>6</sup>.

**Pellet with swim up method :** The semen sample was mixed with equal amounts of sperm wash medium and centrifuged at 1500rpm for 10minutes. The supernatant was discarded and 0.5-0.7ml of media was overlaid on the pellet and the tube was inclined at an angle of about 45° and incubated for 30-45mins at 37 °C. The topmost 0.4ml was removed and sperm count and motility were assessed and used for insemination.

Urine pregnancy test was done 3 weeks after the IUI for diagnosis of pregnancy. A clinical pregnancy was defined as presence of foetal heart by ultrasound scan done two weeks after a positive urine test.

## Results

A total of 518 cycles were studied retrospectively of which 73 resulted in pregnancies giving an overall pregnancy rate of 13.5%. The median age of the women, duration of infertility and endometrial thickness associated with pregnancy was 29.5, 4.75 and 9.65, respectively (Table 1). The indication for infertility (male and female causes) along with the associated pregnancy rates are as shown in Table 3. There was no statistically significant difference in pregnancy rates among different age groups of women under 40years and type of infertility. The 1st and 2nd IUI cycles yielded pregnancy rates of 13.6% and 14.2%, respectively. A maximum of 5 IUI cycles were performed totally, however, no pregnancies occurred after the 4th cycle.

The median sperm concentration observed on analysis of pre-wash sample was 49.5 with a progressive motility of 34.5 (Table 2). A summary of some of the clinical parameters and sperm parameters along with their associated pregnancy rates are presented in Tables 4 and 5.

The statistical calculations were done with the help of SPSS software. A p value of <0.05 was considered statistically significant(S) and any value greater than that (p >0.05) was considered as not significant(NS).

## Discussion

Intra uterine insemination is a relatively simpler and less-expensive treatment for infertile couples (except severe male factor and bilateral tubal block) with the pregnancy rates around the world between 10-20%<sup>7</sup>. This is because of multiple variables involved in an IUI cycle which influence its outcome. In our study we attempted to determine the sperm variables predictive of IUI success.

In this study, it was seen that there were no significant difference in the pregnancy rates among different age groups of women under 40years, type of infertility, duration of infertility (until 12years), number of cycles (1-4cycles) or the endometrial thickness b(7-13mm). This is in concurrence with studies done by Brzechffa et al,1998 and Goverde et al, 2000<sup>8,9</sup>.

While IVF/ICSI is the preferred mode of treatment for severe male factor infertility, IUI has been proven as a treatment modality for mild to moderate male subfertility<sup>2</sup> with good female factors. The three main sperm parameters are sperm concentration, motility and morphology, along with it were considered post wash total motile sperm concentration (TMSC – volume of inseminate x sperm concentration x motility) and method of processing.

In the pre-wash parameters, the initial sperm concentration in the native semen sample is not frequently cited in literature as an influential factor in

an IUI cycle<sup>3</sup>. In a study by Dorjpurev et al, it was seen that the initial sperm concentration of >20 or <20mil/ml did not make a difference to the pregnancy rates<sup>10</sup>. Also, a study by Zadehmodarres in 2009, studied 350 cycles showing no difference among initial sperm concentration and pregnancy rate<sup>11</sup>. In our study too, there was no statistical difference in the pregnancy rates among different groups of sperm concentration unless the concentration was less than 1mil/ml.

**Table 4:** Few clinical parameters and associated pregnancy rates

Clinical Parameters	Pregnancy in percentage (%)	p value
<b>Type of infertility:</b> Primary infertility Secondary infertility	12.7 16.4	0.35
<b>No. of cycles :</b> I II III IV V	13.6 14.2 8.5 21.4 0	0.86 0.33 0.41 1.00
<b>Endometrial Thickness (mm):</b> <7 7.1-9.0 9.1-11.0 11.1-13.0 >13	3.7 14.6 14.5 9.8 18.2	0.14 0.15 0.34 0.17

Significant p < 0.05; Not significant p > 0.05

**Table 5:** Sperm parameters and associated pregnancy rates

Sperm Parameters	Pregnancy in percentage (%)	p value
<b>Pre-wash Sperm concentration (mil/ml):</b> ≤1-5 6-10 11-15 >15	5 2.9 5.3 15.6	0.22 0.07 0.10
<b>Pre-wash Progressive motility (%):</b> <32 >32	11 14.6	0.26
<b>Morphology (%):</b> ≤3 >3	3.5 14.2	0.02
<b>Post wash count(mil/ml):</b> <5 >5	15.2 13.1	0.59
<b>Method of processing:</b> Density gradient Direct swim-up Pellet & swim-up	12.5 14.7 11	0.55 0.61

Significant p < 0.05; Not significant p > 0.05

Studies by Lee et al, 2002, Yalti et al, 2004 and Dorjpurev et al 2011, have observed better pregnancy rates when total motility was >30%,<sup>10,12,13</sup>. In the study by Dorjpurev, 1773 cycles were studied in which it was observed that the pregnancy rate per cycle (9.3%) improved significantly when the motility was >30% (p = 0.001)<sup>10</sup>. This was contrary to our findings wherein motility as an independent factor had no positive influence on the treatment outcome.

A number of studies have shown that of all the sperm parameters, sperm morphology is the positive predictor in an IUI cycle<sup>3,4,5,10</sup>. The study by Nikhbakht et al, took a sperm morphology threshold value as 5% above which they observed higher pregnancy rates<sup>5</sup>. A systematic review by Ombelet in 2013 cited sufficient evidence stating that sperm morphology of >4% is a significant predictor of an IUI outcome<sup>3</sup>. Similar findings were noticed in our study wherein morphology as an independent variable had a statistically significant prognostic value (p=0.024) in an IUI cycle, in comparison to sperm concentration and motility. Significantly higher pregnancy rates were observed with morphology of >3%.

In the post-wash sperm parameters, total motile sperm count (TMSC) is the most commonly cited predictor of an IUI outcome. In a study by Khalil et al., in 2001, that involved 2473 cycles, a TMSC of >5mil/ml or <5mil/ml gave pregnancy rates of 12.8% and 5.3%, respectively; it was stated that TMSC was one the best predictors for pregnancy in an IUI cycle<sup>14</sup>. Even a study conducted by Wainer et al, 2004 stated TMSC of >5mil/ml being a predictor of pregnancy<sup>4</sup>. But in our study the pregnancy rates among both the groups were similar and therefore did not seem to have a significant positive influence as long as the total insemination count was >1mil/ml; there were no pregnancies with post-wash concentration of <1mil/ml.

So far, there have been no studies establishing the effectiveness of any one method of processing for an IUI treatment and therefore no consensus has been reached<sup>7</sup>. Boomsma et al in 2007 conducted a Cochrane database systematic review of the effectiveness of gradient, swim up and wash and centrifugation method. It was concluded that no specific technique could be recommended as sufficient evidence on clinical outcome was lacking<sup>15</sup>.

## Conclusion

On evaluation of the sperm parameters, the pre-wash sperm concentration, progressive motility, the post-wash total motile sperm count and the method of processing the semen sample did not seem to influence the pregnancy rate significantly. However, the sperm morphology as an independent variable has shown to be a positive predictor of IUI success. It can be inferred that in cases of teratozoospermia (≤3%), patients can be counseled for IVF/ICSI as IUI may not be an effective mode of treatment.

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Authors declare no conflict of interest.

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# Original Article

## Leucocytospermia –does it mean anything?

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### Abstract

Leucocytospermia is the nomenclature given to semen sample containing more than 1 mill/ml leucocytes. This is often considered to be a sign of infection and patients are given broad spectrum antibiotics. The objective of this study is to find out the significance of leucocytes in semen samples of patients attending our infertility clinic. **Design:** It is a retrospective observational study. **Setting:** Dept of Reproductive Medicine, Chettinad Hospital, Chennai (August 2009 - July 2011). **Patients:** All patients who came for routine semen analysis and had round cells more than 5 mill/ml were assessed. This study was a retrospective study done with records available in the department of reproductive medicine and not involving the patients directly. Hence Institutional review board (IRB) approval was not required and therefore was not obtained. **Main outcome measures:** The semen samples of such patients with > 5mill/ml round cells were subjected to peroxidase test and those who had leucocytes more than 1 mill/ml were checked for seminal infections through semen culture reports and antibiotic treatments, if any.

**Results:** Among the 2447 patients who came for routine semen analysis, 196 had round cells more than 5 mill/ml with an incidence of 8%. All the 196 patients were tested for leucocytes using peroxidase test and 39 tested positive for leucocytes more than 1 million/ml (39/196=19.89%). These 39 patients were advised semen culture, and only 23 had semen culture done. Seven of them were reported culture positive (incidence of 30.43% i.e. 7/23). The remaining 16 had no growth of any pathogens. Among the 7 with a positive culture report, one showed significant growth, and 2 had moderate growth. They were put on antibiotics after discussion with the microbiologist. Most of them were asymptomatic except for one patient who complained of burning micturition. His urine culture was also positive for the same organism. Four of the patients had very minimal growth and were not treated with antibiotics.

**Conclusion:** According to this observational study, leucocytospermia was not associated with clinical symptoms or bacteriospermia as the culture yielded no growth or insignificant growth of any organisms in majority of the patients.

**Key Words:** Leucocytes, Round cells, Bacteriospermia

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### Introduction

Semen analysis is a valuable diagnostic tool which guides us to choose the treatment modality in male infertility. Routine semen analysis includes the estimation of round cells in semen which may be epithelial cells, immature germ cells or white blood cells<sup>1</sup>. When round cells by routine semen analysis are more than 5 million /ml, then their identity has to be established by peroxidase test.

The reagent used for peroxidase test contains H<sub>2</sub>O<sub>2</sub> and DAB (diaminobenzidine-an indicator). The principle behind this is the oxidation of DAB by H<sub>2</sub>O<sub>2</sub>, in the presence of peroxidase enzyme that is present in the leucocytes. Oxidation is indicated by the colour change of the round cells from pink to brown.

H<sub>2</sub>O<sub>2</sub> + DAB (pink) → oxidized-DAB (brown)

According to WHO 2010 guidelines, Leucocytospermia is defined as the presence of more than 1 mill/ml leucocytes in the semen sample<sup>2</sup>. However whether the presence of leucocytes in the semen sample is pathological or physiological is still debatable. The question whether it indicates a normal function or a

clinical infection is yet to be answered as it is seen in 10% of fertile men also<sup>3</sup>.

Studies have shown that even at high concentrations, presence of leucocytes alters neither sperm fertilization ability nor the probability of clinical pregnancy in fertile men. Even ART outcomes are not influenced by the presence of leucocytospermia<sup>3</sup>.

However, it is common knowledge that leucocytospermia produces Reactive oxygen species which in combination with nitric oxide causes peroxidative damage to the plasma membrane and DNA integrity and thereby interferes with fertilizing capacity and motility of spermatozoa<sup>4,5</sup>.

In concurrence to this, there is reported increase in the incidence of leucocytospermia among infertile men, ranging from 15-28%, with or without associated In concurrence to this, there is reported increase in the incidence of leucocytospermia among infertile men, ranging from 15-28%, with or without associated symptoms<sup>6</sup>. With the background of contradictory evidences regarding the physiological or pathological significance of leucocytospermia, this observational

study was conducted in order to find out the role of leucocytes in semen samples of infertile patients.

## Methodology

It is a retrospective observational study done in the Dept of Reproductive Medicine, Chettinad Hospital, Chennai. This study was a retrospective study done with records available in the department of reproductive medicine and not involving the patients directly. Hence Institutional review board (IRB) approval was not required and therefore was not obtained.

## Data collection

Data of patients who had round cells more than 5 mill/ml in a routine semen analysis from August 2009 - July 2011 were included in this study. The data of semen culture reports and subsequent antibiotic treatment for patients who had leucocytes more than 1 mill/ml by peroxidase test was noted and analyzed.

## Results

Among the 2447 patients who came for semen analysis 196 had round cells more than 5 mill/ml giving an incidence of 8%. All the 196 patients were tested for leucocytes using peroxidase test and 39 had leucocytospermia (39/196=19.89%). These 39 patients were advised semen culture, but only 23 were compliant. Among the 23, only seven had reported culture positive. The remaining 16 had no growth of any pathogens. Among the 7, one showed significant growth, and 2 had moderate growth. They were treated with antibiotics after discussion with microbiologist though they were asymptomatic except one whose urine culture had the same organism. Four patients had very minimal growth and were not treated with antibiotics. One of the patients who showed cultured negative underwent an ART cycle (ICSI) resulting in the birth of a healthy girl baby.

## Discussion

Leucocytospermia need not always be pathological but can also be physiological, as not all leucocytes are associated with infection. Though bacterial growth is seen in samples with leucocytospermia, this could be attributed to contamination of the semen sample with bacterial flora from the skin, prepuce, hands, urethral meatus and urine<sup>7</sup>. Leucocytospermia does not necessarily mean infection. Approximately 80% of patients with leucocytospermia do not have bacteriospermia<sup>8</sup> and even normozoospermic patients sometimes show growth of pathogens in semen culture<sup>9</sup>. Leucocytes usually originate from epididymis but the origin of the leucocytes in men with leucocytospermia is not clear<sup>8</sup>. Sometimes leucocytospermia can be associated with urinary tract infection. When asymptomatic bacteruria is not treated with antibiotics, then it seems unnecessary to treat patients with asymptomatic leucocytospermia. Few studies have found that leucocytes count in semen samples shows intra-individual variations with one analysis showing >1 mill/ml leucocytes vis-a-vis another with none<sup>10</sup>. So empirical therapy with antibiotics for leucocytospermia is not necessary. A repeat semen analysis, semen culture and a urine culture (if the patient is

symptomatic) will help to treat the patient more efficiently than empirical therapy with antibiotics.

The correlation of leucocytospermia with infertility, if any, could not be deduced from this study due to its small size. Larger randomized studies will help to understand the influence of leucocytospermia on infertility and whether treatment with antibiotics is beneficial in such cases.

## Conclusion

According to this observational study, leucocytospermia defined as leucocytes more than 1 mill/ml (WHO 2010) was not associated with clinical symptoms or bacteriospermia by culture. So larger studies are required to see if leucocytospermia is an indicator of infection in the male and its influence on fertility. However, our study has shown that empirical therapy with antibiotics is not necessary in asymptomatic leucocytospermia.

**Acknowledgement :** We thank Mr. Kartheeswaran for his help.

**Authors declare no conflict of interest.**

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**National Apex Committee for Stem Cell Research and Therapy (NAC – SCRT) joins forces with ASCI, India (Mumbai, Feb 10, 2015).**

The National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) joins hands with Advertising Standards Council of India (ASCI) to monitor advertisements that claim stem cell based therapies. As per the National Guidelines for Stem Cell Research- 2013 there are no approved indications for stem cell therapy other than the Hematopoietic Stem Cell Transplantation (HSCT) for haematological disorders. NAC-SCRT has observed that several clinicians / companies / hospitals advertise stem cell based therapies other than haematopoietic stem cell transplantation for haematological disorders on their websites. These therapies are currently investigational and must be conducted only within the scope of clinical trials. Such misleading advertisements are to be removed and action be taken against the defaulters unless they are suitably modified to clarify the unproven nature of these therapies.

Prof. Alok Srivastava, Chairman, NAC-SCRT has clearly stated that such advertisements are in violation of the clause 10.3.1 of the National Guidelines for Stem Cell Research-2013. Use of stem cells for any other purpose outside the ambit of clinical trials will be against these guidelines and is hence not permissible. ASCI has already initiated action against 23 such websites. It is good to note that several advertisers have immediately started amending the web-site content.

**- Prof. RM. Pitchappan**

# Review Article

## Lifestyle And Environmental Factors Influencing Male Fertility

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### Abstract

The decline in the quality of semen parameters over the last few decades can be partly attributed to lifestyle and environmental factors. Recent trends in lifestyle including sedentary jobs, obesity, smoking, alcohol consumption, recreational drug abuse along with environmental factors like pollution and toxic chemical substances have been found to have adverse effects on the functional capacity of spermatozoa thereby impairing male fertility. A positive change in quality of life like healthy dietary habits, regular physical exercise and avoidance of smoking, alcohol intake and recreational drug abuse may reduce the damage incurred to the spermatozoa, thereby increasing the male fertility potential.

**Key Words:** Male infertility, Lifestyle, Environment, Altered spermatogenesis, Impaired function

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### Introduction

The last few decades have seen a substantial decline in the quality of semen parameters<sup>1,2</sup>. This phenomenon may be partly attributed to the changes in the lifestyle factors and environmental changes. The lifestyle factors that influence male fertility include smoking, alcohol consumption, recreational drug use, stress, radiation, improper dietary habits and lack of physical activity leading to obesity. Environmental factors influencing male fertility include seasonal temperature variations and other occupational exposures. This review article aims to understand the mechanisms by which these lifestyle and environmental factors negatively influence male fertility.

### Effects of Temperature

Environment plays a very significant role in male fertility as it is well established that normal spermatozoa functions are affected by environmental changes<sup>3</sup>. In men, normal spermatogenic functions of the testis require the scrotal temperature to be steadily kept 2 - 2.5°C lower than the normal core body temperature. This thermoregulatory mechanism is maintained by the pampiniform plexus which acts as a counter current heat exchanger and by the scrotal dissipation of heat.

Persistent exposure to factors that compromise the thermoregulation capacity of the scrotum causes elevated scrotal temperature resulting in failure of spermatogenesis and reduced sperm numbers in the ejaculate<sup>4,5</sup>. Current day jobs, most of which are sedentary result in reduced air flow around the scrotum, leading to overheating in the same area and it has been suggested that this may have a significant adverse effect on the quality of spermatozoa that are produced<sup>6,7</sup>.

Long distance truck drivers, foundry workers, furnace workers, bakers, welders and those working in metal, glass and ceramic industries are particularly vulnerable to heat exposure. Continuous monitoring of temperature has revealed that scrotal temperature increases by 1.7°C -2.2°C within 2 hours of starting to drive a car<sup>5,7</sup>. These effects are also seen in paraplegic men who are confined to wheelchairs<sup>8</sup>.

However, the extent to which elevated scrotal temperature affects semen parameters is dependent on both the degree and duration of temperature elevation. Frequent scrotal exposures to relatively higher temperatures of >40°C (hot baths) for 20 minutes or more has higher chances of causing damage than smaller elevations in scrotal temperature (0.5°C-1.0°C)<sup>9</sup>. Frequent sauna baths, wearing of tight underwear for long duration of time and increased scrotal thickness which is seen in conditions such as elephantiasis of scrotum can also interfere with the thermoregulatory mechanism of the scrotum and thus cause spermatogenic abnormalities<sup>10</sup>.

Climatic variations could play an important role in sperm production as seasonal variations in sperm counts have been reported<sup>11</sup>. Reduced sperm concentrations have been consistently reported in the summer months which could be an indication of the adverse effect of the higher summer temperatures on sperm production<sup>12</sup>.

### Effects of Obesity

An increased likelihood of abnormal semen parameters like decreased spermatogenesis, poor sperm quality and reduced normal sperm morphology have been observed in men who are overweight thereby resulting in decreased fertility. Obesity thus should be considered as an important etiology of male infertility<sup>13</sup>.

Obesity is also a direct result of emergent sedentary life style habits in young men<sup>14</sup>.

A Body Mass Index (BMI) of  $>25$  kg/m<sup>2</sup> has been shown to be negatively associated with sperm quality. For every 10 kilogram increase in a man's body weight above the corresponding normal weight, the chance of fertility is reduced by about 10%. Also, for every three point increase in the BMI, the risk of infertility increases by about 12%<sup>15</sup>.

The principal cellular constituents of adipose or fatty tissue are adipocytes whose proliferation is stimulated by estrogen while testosterone inhibits it. Also, adipocytes convert androgens to estrogens with the help of the enzyme aromatase. Hence, an increase in the adipose tissue mass causes an elevation in the circulating estradiol levels which in turn suppresses the Hypothalamus-Pituitary-Testicular axis, thereby reducing testosterone levels. The reduced testosterone levels further contributes to increased abdominal adipose tissue thus completing a vicious cycle.

Leptin, a hormone produced by fat cells is believed to play a role in the regulation of normal male reproduction. Male obesity is characterised by increased levels of leptin and hence leptin acts as a link between obesity and male infertility. Studies have shown the presence of leptin receptors in male germ cells, implicating its role in cell proliferation and differentiation<sup>16</sup>. It is believed that high leptin levels can disturb spermatocyte development and differentiation. A high leptin level also produces hypogonadism, reduces testosterone levels and induces testicular apoptosis<sup>17</sup>.

Obese men also carry the risk of testicular heat stress due to the accumulation of suprapubic and inner thigh adipose tissue<sup>18</sup>.

## Effects of Occupational Exposure

Men exposed to hazardous work environments which include handling of toxic or harmful chemical substances and radiations, run an increased risk than the general population of incurring damage to their sperms. Lead poisoning in battery plant workers can lead to fibrosis around the seminiferous tubules causing testicular damage<sup>19</sup>. Metals like cadmium, chromium and manganese can affect sperm motility and the effects are more so in steel welders who are exposed to these metals in larger amounts<sup>20</sup>.

Studies have reported decreased sperm motility and vitality in men working at toll booths and traffic policemen who are exposed to pollutants like nitrous oxide, sulphur oxide and carbon monoxide at significantly high levels<sup>19</sup>. Agricultural workers exposed to insecticides, pesticides (e.g., carbamates), Dibromochloropropane (agricultural soil fumigant) and workers in synthetic rubber industries(exposed to the plastic monomer chlorprene) have also been found to have low sperm counts<sup>21,22</sup>.

## Effects of Alcohol

The effects of alcohol were known way back in the

Elizabethan era when William Shakespeare rightly said, "Alcohol provokes the desire but takes away the performance" when describing the power of alcohol in relation to sexual function. Few of the ill effects of alcohol are decreased libido and disruption of normal spermatogenesis due to its effect on the pituitary or hormonal levels. Evidence suggests that alcohol can impair testosterone production and can cause shrinkage of testicular volume and also hinder erection<sup>23</sup>. To demonstrate the adverse effects of alcohol, a study was conducted among volunteers with normal liver function, who were administered 15% solution of alcohol every 3 hours over a 4 week period along with diet containing proteins, vitamins, folic acid and minerals and was found that there was a decline in testosterone levels<sup>24</sup>. Alcohol also disrupts normal spermatogenesis which has been shown in autopsy findings of alcoholics<sup>25,26</sup>. However, the exact mechanism by which alcohol affects sertoli cells and disrupts the normal functions is unknown<sup>27</sup>.

Excessive intake of alcohol also disturbs the hypo-thalamo-pituitary function, further worsening testicular and sexual function. Sexual dysfunction is a well-known consequence of alcoholism, as are the signs of hyperestrogenism which is probably secondary to disturbances of testosterone and estrogens metabolism in the cirrhotic liver<sup>28,29</sup>. Advancing age, decline in testosterone levels and increases in gonadotrophin levels are associated with a decrease in sperm production and number of normal sperm<sup>30</sup>.

## Effects of Smoking

"Cigarette smoking is injurious to health" is a statutory warning printed on all cigarette packets across the world in spite of which, number of smokers are steadily increasing worldwide. The effects of smoking, either active or passive or through third hand smoke (present in the environment), affects the respiratory, cardiovascular and reproductive system and produces various pathologies. It is of particular concern to the reproductive system as it affects the semen parameters.

Spermatozoa produced in men who smoke have reduced fertilising capacity and also produce defective embryos which have lower implantation rates. These occurrences are difficult to substantiate with evidence but a number of follow up studies have shown the lower implantation potential due to aneuploidy<sup>31-33</sup>.

Numerous authors have found a negative impact of smoking on human semen parameters negatively correlating with the number of cigarettes smoked per day and particularly the duration of smoking. Some authors have clearly stated that smokers demonstrate lower semen volume, sperm concentration, sperm motility and viability compared with non-smokers. They have also found that these semen shown an increased seminal leukocyte count and an increased incidence of globozoospermia<sup>34-38</sup>.

The causes for fertilization failure or poor implantation potential can be due to acrosomal damage or DNA damage during spermiogenesis<sup>39,40</sup>. Studies found that sperm DNA fragmentation in smokers is

demonstrably high when compared with non-smokers<sup>41</sup>.

The hypo-thalamo-pituitary axis can be altered by nicotine through stimulation of growth hormone, cortisol, vasopressin and oxytocin release, which indirectly inhibit release of LH and prolactin.

Ochedalski et al reported that the mean level of 17 beta-estradiol was higher and the mean levels of LH, FSH and prolactin were found to be lower in smokers when compared with non-smokers, while the mean levels of testosterone and dehydroepiandrosterone did not differ<sup>42</sup>. Increased free and total serum testosterone and decreased prolactin levels were observed in smokers<sup>43</sup>.

The function of accessory sex glands in smokers has been assessed by determining the various glandular markers in the ejaculate such as N-acetyl amino sugar, total phosphate, zinc, acid phosphatase, and alpha-1,4-glucosidase. Both the vesicular and prostatic parameters were significantly lowered in smokers<sup>44</sup>.

The seminal ejaculates of smokers are varied in comparison to non-smokers, with the presence of Detached Ciliary Tufts (DCTs) and mast cells. Bornman et al, hypothesized that DCTs which originate from the epididymal epithelium may be shed as a result of testicular pathology and their presence has been demonstrated in the semen of smokers<sup>45</sup>. It has been shown that the seminal mast cells detected at higher frequency among smokers lead to reduced progressive motility of spermatozoa<sup>46</sup>.

### Effects of illicit drugs

The illicit drugs that can cause male infertility include marijuana, cocaine, methamphetamines, opioid narcotics and anabolic-androgenic steroids. These drugs are often abused by men during the reproductive years leading to compromised fertility.

Marijuana, when smoked releases a psychoactive cannabinoid compound called delta-9-tetrahydrocannabinol (THC). THC acts on the receptors present in the sperm middle piece and inhibit its mitochondrial activity resulting in reduced sperm motility<sup>47,48</sup>. Methamphetamines are associated with an increased incidence of sperm DNA damage<sup>49</sup>.

Anabolic-Androgenic Steroids are the most commonly abused drugs by sportsmen for performance enhancement. AAS users often take supraphysiological doses of testosterone which are 50 to 100 times greater than the normal production<sup>50</sup>. These exert a negative feedback on FSH, LH and endogenous testosterone secretion thereby impairing sperm concentrations<sup>51</sup>.

### Effects of stress

Though the impact of stress on infertility still remains unestablished, its aetiology cannot be completely overlooked. Several studies have stated that sperm motility and morphology are reduced due to emotional stress. One of the mechanisms could be due to negative impact on the pituitary gonadal axis thereby resulting in decreased sperm concentration and motility<sup>52</sup>.

A study done in Turkey by Eskiocak, on 27 normal healthy men found that the activities of antioxidant enzymes present in semen like superoxide dismutase and catalase were increased when stress levels were high leading to increased production of free radicals. This increase can negatively impact the sperm parameters, mainly motility<sup>53</sup>.

Another important factor to be taken into consideration is the influence of stress on autonomous nervous system which in turn is responsible for ejaculation of semen. So, increased stress can cause decreased semen volume and also reduced sperm motility<sup>54</sup>.

### Effects of radiation

The cells in the human body, especially germ cells and Leydig cells are sensitive to different kinds of radiation including X-rays, gamma rays and mobile phone radiations. Numerous studies have established the impaired effects of radiofrequency electromagnetic waves (RF-EMWs) on sperm motility which act either through production of heat or through radiations, but which of the two has greater negative impact on semen quality still remains to be established. The thermal effects are most likely to affect sperm concentration as prolonged usage of mobile phones while placed in the trouser pocket, increases the scrotal temperature. The radiations (non-thermal) have been known to affect sperm motility and vitality<sup>55-57</sup>. Studies have also stated that there is an increase in DNA fragmentation due to increased reactive oxygen species production, one of the damages caused by radiation<sup>58</sup>.

### Conclusion

Apart from genetic, infectious, hormonal and idiopathic causes, male infertility due to lifestyle and environmental factors is an area of increasing concern. If the trends of increased smoking, alcohol intake and recreational drug use continue along with increasing trends in obesity, it is highly probable that male fertility could be severely compromised in the population in the years to come. However, with changes in lifestyle such as healthy dietary habits, regular physical exercise and avoidance of smoking, alcohol intake and recreational drug abuse, this can be prevented to a certain extent.

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# Review with Hypothesis

## The Undescended Testis – A Review with Hypothesis

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### Abstract

Testicular Descent is enigmatic in the sense the exact interaction between anatomical, hormonal and molecular factors coordinating the various phases of descent remains to be elucidated. This review explores testicular descent in various species along with anatomical and hormonal factors regulating descent. But why does the testis not descend? Both bilateral and unilateral undescended testis has an effect on the individual's future fertility. We have reviewed the literature and presented briefly on the various causes that could lead to testicular undescend. Lastly we have also given a hypothesis that could account for testicular undescend.

**Key Words:** AMH, Gubernaculum, INSL3, Cryptorchidism

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Descent of the testes is a complex multistep event well orchestrated in time and space descent. It is a process during which the testes move from a high abdominal pararenal position to an extra-abdominal position. Despite our excellent understanding about the mammalian testis and its function, the complex interplay between anatomical, hormonal, genetic and mechanical factors involved in descent of testes remains to be elucidated.

### A. Testes Descent in Various Species

Testes descent does not take place uniformly across all mammalian species. Absence of descent also is seen among the ancient evolutionary mammalian species of Monotremata, Edentata, the aquatic species of Cetaceans and of Peningulata (Elephant and Hyrax). In Cetaceans, secondary; as an adaption to aquatic environments, whereas in species of Peningulata, it is primary<sup>1</sup>. Progressively through evolution however the testis has acquired a position lower and lower, finally coming to be placed in a specialized sac called the scrotum which provides a temperature of 33 degree Celsius which is lower than the rest of the body<sup>2</sup> (34 – 37°C). The high temperature sensitivity of the testes and its effect on the germ cell development and Sertoli cell function is well documented in the literature through experiments on various animal models; however, the exact genetic basis of this regulation is yet unknown<sup>3, 4</sup>. The most interesting question to ask though is, 'Why does the testis descend at all in man?' Descent does not seem to offer any particular advantage, but rather puts the testis in a vulnerable position; does the testes search out and seek a lower temperature?

The timing of testes decent varies considerably among mammals. At birth testes descent is generally complete in humans, pigs, rabbits and horses. In cattle and deer, descent is complete early in gestation, whereas in mouse and dogs, the descent takes place after birth<sup>5</sup>. Across most of these species, two phases of testicular descent namely, an abdominal phase and an inguino- scrotal phase are distinctly observed.

### B. Timeline of Testis Development

During fetal life, the formation of the bipotential gonad takes place between the 5th and 6th week. At this point of time, primordial germ cells (PGC) arising from the endoderm of the yolk sac migrate to genital ridge that is present medial to the mesonephros. The PGC differentiate into gonocytes. Activation of the SRY gene along with *wt1*, *sox9*, *fgf9* and *sf1*, leads to the formation of Sertoli cells from the coeloemic epithelium<sup>6</sup>. The Sertoli cells surround the gonocytes giving rise to testicular cords between 6 and 7 weeks, and this marks the first sign of sexual differentiation in the ambisexual gonad<sup>6,7,8</sup>. By 9 weeks steroid secreting Leydig cells are formed. Antimullerian hormone (AMH) produced by the Sertoli cells causes the mullerian duct to regress which otherwise would lead to formation of female internal reproductive organs, while testosterone produced by the Leydig cells stabilizes the Wolffian duct and causes it to differentiate into male reproductive organs. Testosterone converted to Dihydrotestosterone (DHT) masculinizes the external genitalia. These events take place between weeks 8 and 12 of gestation<sup>9</sup>.

### C. The Gubernaculum's role in testis descent – Anatomical factors

Between 7 and 9 weeks the connection between the mesonephros and testes disappears. The metanephros (final kidney) migrates from sacral to lumbar region causing a displacement of the gonad caudal to the kidney<sup>10</sup>. Testis descent in humans takes place in two phases, in the first phase the swollen gubernaculum anchors the testis to the inguinal region, while the abdomen is enlarging. This is the relative trans-abdominal phase of testis movement. The ovary on the other hand moves cranially, relatively speaking of course. Simultaneously, regression of the cranial suspensory ligament allows the testis to descend. In humans, the first phase of descent is usually complete by 15 weeks<sup>11</sup>.

John Hunter and Von Haller first described the gubernaculum as a fibrous cord connecting the testis with the scrotum<sup>12,13</sup>. The gubernaculum contains predominantly mesenchymal cells in man. Enlargement of the gubernaculum also termed, as the 'swelling reaction', is due to an increase in cell division and hyaluronic acid content<sup>14</sup>. During descent, the proximal portion of the gubernaculum incorporates into the bulb, thereby placing the testis at close proximity to the inguinal ring, following which an increase in the abdominal pressure may push the testis out of the abdomen<sup>15,16,17</sup>. Studies in various animal models have shown the aforementioned mechanism of gubernacular shortening to be an important mechanism in testis descent, as transection of the cord leads to aberrant gonad position at various abdominal sites<sup>17</sup>. In mice with mutations of *hoxa10* gene, abnormally long gubernacular cords along with undescended testis are seen<sup>18</sup>. *hoxa10* is growth regulatory gene, expressed in developing limb buds<sup>19</sup>. The gubernaculum is likened to a limb bud that guides the testis to reach its position. Although the cranial suspensory ligament regresses to allow gonad descent, its role as the key factor in allowing descent is under dispute.

The second phase of descent, termed as the inguinoscrotal phase, requires the testis to be anchored near the internal inguinal ring, followed by active growth and enlargement of the gubernaculum with the processes vaginalis. An absolute increase in the wet mass of the gubernaculum, compared to testis is noted. This causes a dilatation of the inguinal canal, thereby allowing the testis, epididymis and gubernaculum to move as a single entity through the inguinal canal. This process is partly aided by an increase in abdominal pressure<sup>20</sup>. Fibrosis and shrinkage of the gubernaculum may also contribute to passage of testis through the inguinal canal. After this phase, the peritoneum pouch of the processes vaginalis ensconces the testis, gubernaculum and epididymis. The gubernacular caudal end does not reach the bottom of the scrotum. Following testis descent to the bottom of the scrotum, the connection to the peritoneum involutes. The gubernaculum shrinks and persists as the scrotal ligament. The inguino-scrotal phase of descent is complete by 35 weeks<sup>20</sup> (Fig 1).

### D. Hormonal Regulation of Testis Descent

**1. Androgens:** Androgens are not required for the first phase of testis descent. Even in patients with complete androgen insensitivity syndrome, in a significant number of patients the testis usually traverses the abdomen<sup>21</sup>. The gubernacular swelling reaction occurs in mouse and humans with complete androgen resistance and in rats that are prenatally exposed to Flutamide<sup>22</sup>. Androgens play an important role in the inguinoscrotal phase of descent. For both gubernacular migration and regression, numerous studies have shown that a high local level of androgens are required, although the exact site of androgen action on the gubernaculum remains to be identified<sup>23</sup>.

In rodents, prenatally androgens may indirectly act on the gubernaculum by a yet unknown mechanism on the genito-femoral nerve nucleus (GFN) to induce a sexually dimorphic GFN nucleus<sup>24</sup>. Since the GFN supplies the gubernaculum from its posterior and caudal surface, transection of the GFN in rodents leads to Cryptorchidism. The GFN along with the neurotransmitter calcitonin gene related peptide (CGRP), are implicated in rodent models of cryptorchidism. A rhythmic increase in Gubernacular contraction both in vivo and in vitro is documented in response to CGRP. Antiandrogen administration in rodents led to alternations in GFN nucleus along with testis maldescent<sup>24,25</sup>. The role of CGRP and GFN in human models of cryptorchidism is less persuasive though. Although children with spina bifida have associated undescended testis, this example is too non-specific<sup>26</sup>.

**2. AMH:** Antimullerian hormone (AMH) or Mullerian inhibiting substance (MIS) produced by Sertoli cells of the testis causes the regression of the embryonic Mullerian duct. In addition, numerous other functions such as the early differentiation of the testis, postnatal germ cell development and the important function of regulating the first phase of testicular descent have been postulated<sup>22</sup>. Evidence for AMH role in regulating the first phase of descent comes from studies in mice models with intra-abdominal testis; these animals have persistent Mullerian ducts. The next evidence comes from the finding that a proportion of retained Mullerian ducts are found associated with cryptorchidism in intersex as well as estrogen treated fetal mice<sup>27</sup>. The third line of evidence comes from the finding that in patients with Persistent Mullerian Duct Syndrome (PMDS), a majority of them present with undescended testis, a long and thin Gubernacular cord and mutation of the MIS gene thereby suggesting that in these patients the Gubernacular swelling reaction failed to occur leading to undescended testis<sup>28</sup>. Evidence against AMH comes from the fact that cultured fibroblasts from pig gubernaculum do not divide in the presence of AMH<sup>29</sup>, raising the question – does AMH cause the Gubernacular swelling? Another important point going against AMH is that in patients with PMDS, non-descent of testis could be a result of anatomical blockade due to a connection between the Mullerian duct and undescended testis<sup>30</sup>.

Furthermore, not all patients with undescended testis present with persistent Mullerian duct remnants.

**3. INSL3:** INSL3, a peptide, plays a crucial role in gubernacular swelling reaction in mice<sup>31</sup>. Disruption of the *insl3* gene leads to bilateral intrabdominal testis and malformed gubernaculum<sup>32</sup>. In female mice, ovaries descend to the inguinal region when INSL3 is over expressed<sup>33</sup>. The role of INSL3 in human testis descent is not clear since only a small minority of patients presenting with unilateral or bilateral cryptorchidism harbor mutations in the *insl3* gene<sup>34</sup>.

which also termed as mini-puberty stimulates the gonocytes to differentiate in to type A spermatogonium. Testosterone levels wane by 6 months; following which AMH levels rise and remain elevated until puberty, and then it falls<sup>46</sup>. The regulation of this complex transformation and event is unknown<sup>46</sup>.

The post-natal germ cell development is impaired in the undescended testis, leading to an increase in the

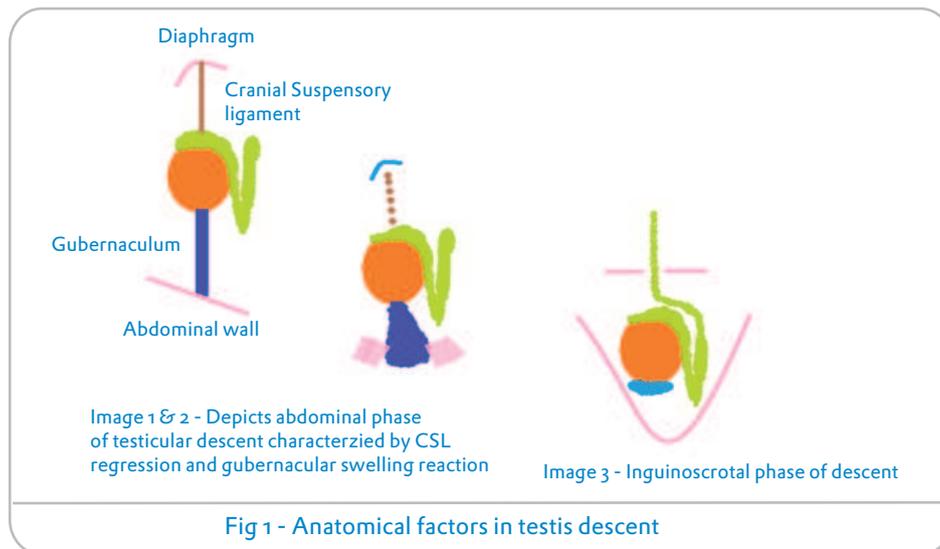


Fig 1 - Anatomical factors in testis descent

## Phases of testis descent

**E. Cryptorchidism:** The incidence of isolated non syndromic congenital cryptorchidism; including only male babies born with a weight greater than 2500 gms in several large series has been estimated to be between 2.2 and 3.8%<sup>35,36</sup>. Among full term males descent takes place spontaneously in 50 -70% usually in the age group of one to three months, although among premature neonates not only is the incidence of cryptorchidism higher, but also the presentation is bilateral with descent occurring at the end of one year<sup>37</sup>. In humans, cryptorchidism occurs due to defects commonly in the inguinoscrotal phase of descent, and only 5% of undescended testes are in the abdominal position<sup>38</sup>. Common causes of cryptorchidism include a defective androgen secretion prenatally, and defects in the placental or pituitary gonadotropin production. The abnormal androgen secretion could affect the development of the GFN nucleus and CGRP production leading to defective gubernacular migration resulting in impaired testicular descent<sup>39</sup>. Infants presenting with urological disorders like prune belly syndrome, posterior urethral valves; abdominal wall defects and neural tube defects also frequently have undescended testis<sup>40,41,42,43</sup>. Corbus reported cryptorchidism among six brothers in a family<sup>44</sup>; Wiles has also reported cryptorchidism among three successive generations of a family<sup>45</sup>, thereby suggesting a familial occurrence of cryptorchidism.

**1. Post Natal Germ Cell Development:** A surge in pituitary gonadotropin causes a sudden increase in testosterone at the age of 2 to 4 months; this process

number of gonocytes, which are pluripotent and may lead to Carcinoma in situ cells (CIS) and ultimately resulting in an increased risk of testicular cancer in the undescended testis<sup>46</sup>. Cryptorchidism affects the germ cells, causing their degeneration and a reduction in their number; thus leading to infertility. A correlation between the numbers of dark type A spermatogonium at three to six months of age and sperm counts after puberty is seen among patients with undescended testis. In animal models, most authors suggest that there is a secondary degeneration of the germ cells owing to the higher intra-abdominal temperatures. In humans, a decrease in the androgen production could affect postnatal germ cell development and germ cell numbers<sup>46</sup> thus suggesting a primary testicular defect. Further serum androgen levels were not measurable in a group of infants with cryptorchidism at 3 months of age<sup>47</sup>.

**2. Histopathological finding in the undescended testis:** Histological findings of the undescended testis reveal varying patterns from Sertoli cell only to normal<sup>48</sup>. This also depends on the extent of descent, age of biopsy or Orchidopexy and duration of cryptorchidism. A rapid decrease in the number of germ cells is found in patients with undescended testis; starting from 6 months until 2 years; further, only less than 10% of patients would have normal number of spermatogonium after 1.5 years of age<sup>10,48,49</sup>. An increasing number of patients by 2 years of age would have essentially no germ cells on histological examinations. Another interesting finding is that, even in the normally descended contra lateral testis; germ cell numbers and testis differentiation is affected to a certain degree<sup>48,49</sup>. The presence of dark

spermatogonium on histological examination is associated with future fertility. In bilateral cryptorchidism, if no germ cells are found there is a 78 – 100% risk of oligozoospermia (sperm count less than 5 million/ml) in adulthood<sup>49</sup>. In cases of bilateral cryptorchidism, we postulate that; a congenital loss of germ cell has already occurred in utero, thereby suggesting a primary testicular defect.

**3. Orchidopexy – is there a need?** - The success of Orchidopexy can best be determined only in cases of bilateral cryptorchidism that are fixed followed by evaluation of the patient's future paternity.

Unfortunately, our literature search revealed only a few studies. Notable among them was a study by Gross and Jewett (1956). The Boston authors had reported that 30 of 38 men who underwent surgery for Bilateral cryptorchidism were fertile. The drawback of the study; was that there was no mention of the testicular position at the time of surgery<sup>50</sup>. In patients presenting with unilateral undescended testis, a major impact on future paternity is not expected.

An increase in the number of cases undergoing an Orchidopexy in recent times is attributable to the retractile or ascending testis. Whether these two clinical entities are the same or different is to be elucidated. Although an impact on future paternity is not expected in either case, it is important to correctly differentiate both entities from true congenital Cryptorchidism<sup>51</sup>.

### Hypothesis and conclusion

The exact mechanism behind the undescended testis is unknown. Animal models of Cryptorchidism cannot be extrapolated to human studies, due to key differences in the timing of development. From our literature review and personal experience, we would like to hypothesize that 'The reason the testis does not descend lies within the testis itself. It is not the undescended testis that is abnormal in its function; rather a testis that is functionally abnormal will not complete its descent'.

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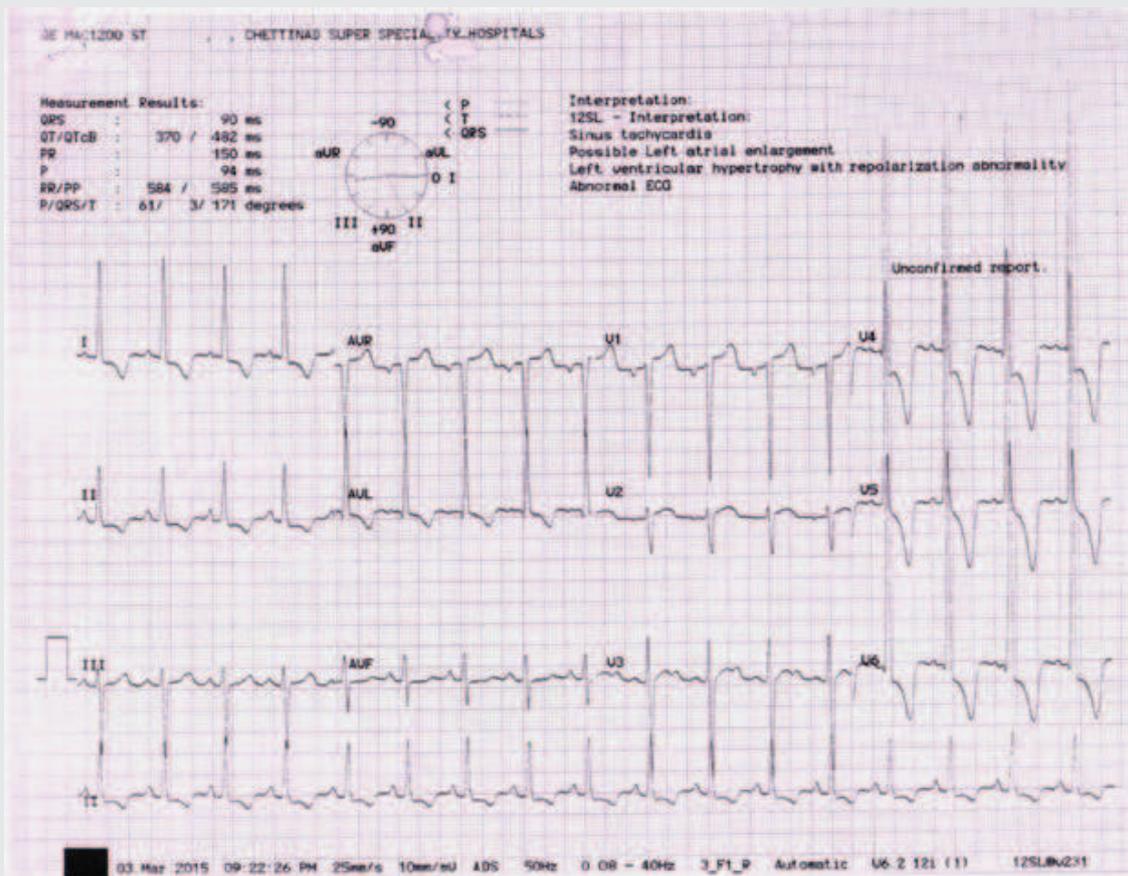
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## Diagnose the condition

24 year old male presented with hypertension to the cardiac clinic.



Dr. M.Chokkalingam, Consultant Cardiology, CSSH.

Answer in page : 180

# Case Report

## Hypogonadotropic Hypogonadism – Canary in a Coal Mine?

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**Key Words:** Hemochromatosis, Hypogonadotropic hypogonadism

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### Introduction

Hypogonadotropic hypogonadism contributes to 15% of anovulatory infertility<sup>1</sup>. Hypogonadotropic hypogonadism is encountered rarely in routine clinical practice and leads to surprises at times as in this case.

### Case report

24 yrs female, reported to the Reproductive Medicine Out Patient Department with history of involuntary childlessness for 3 yrs. She attained spontaneous menarche at 13 yrs. Initial cycles were regular, later it became irregular with a cycle length of 60-90 days. Since three years she had withdrawal cycles with combined pills. She was a known case of diabetes mellitus diagnosed one year ago for which she was on oral hypoglycaemic agent and insulin. Glycaemic control was suboptimal despite compliance to medication. No significant parental/sibling history.

Laparoscopy of pelvis done elsewhere showed a small uterus with bilateral patent tubes. Ovaries were reported as small and atrophic. No further comments about the pelvic findings were available. Her investigations done 12 months before presentation to us were supportive of hypogonadotropic hypogonadism with low levels of serum FSH (0.2mIU/mL) and LH(0.3mIU/mL). Thyroid status was reported as normal. Cytogenetic analysis revealed a normal karyotype. Her male partner was normozoospermic.

On examination, her height was 153 cm and weight was 52 kg with a BMI of 22. General examination and other systems examination were normal. Secondary sexual characters were as follows- Axillary hair –Tanner's stage 1, Pubic hair –Tanner's 3, Breast –Tanner's 4. On pelvic examination a small uterus and cervix was palpable through a narrow vagina. USG pelvis confirmed a hypoplastic uterus with an endometrial thickness of 2.8 mm. Right ovary measured 13x12mm, no antral follicles, left ovary measured 16x18mm with 1-2 antral follicles.

With the diagnosis of anovulation secondary to hypogonadotropic hypogonadism, ovulation induction with gonadotrophins was considered. Investigations were repeated at our centre before ovarian stimulation on 17.11.2013 (Table 1).

Hb	11 gms%	(12-16gm/dL)
PCV	33.27%	(36-47%)
Blood Sugar		
Fasting	202 mg%,	(70-105mg/dL)
Postprandial	306mg%	(<140mg/dL)
HbA <sub>1c</sub>	9.1%	(4.7-8.5%)
TSH	1.21 mIU/ml	(0.5-5mIU/mL)
Prolactin	11.4 µg/ml	(<20 µg/L)
Serum FSH	0.23mIU/ml	(5-20mIU/mL)
Serum LH	0.27mIU/ml	(5-22 mIU/mL)
Estradiol level	50pmol/L	(50-100pmol/L)

Viral Screening for HIV, HbsAg, Hep C-Negative, Rubella – Protected. Gonadotropins were started in a low dose step up fashion for ovulation induction after confirmation of diagnosis. As the risk of hyperstimulation is high in these women, human menopausal gonadotropin 37.5 IU was started and stepped up to 75 units. The dosage was further increased to 150IU and was abandoned after 39 days due to non responding ovaries.

On further work up, she had an MRI pituitary fossa which showed a hypoplastic anterior pituitary (fig 1&2). There was diffuse hypointensity on GRE images in choroid plexus of bilateral lateral ventricles, foramen of Luschka and Magendie, suggestive of haemosiderin deposits, differential diagnosis being-Haemosiderosis which could be secondary to Thalassaemia, Wilsons disease, Amiodarone or colloidal gold administration.

Her liver enzymes were elevated. Serum iron, ferritin, transferrin saturation were very high (table 2). Her ceruloplasmin levels were normal and there was no history of administration of Amiodarone or colloidal gold. All these features were suggestive of primary haemochromatosis with secondary hypogonadism and diabetes. Mutation analysis was inconclusive (Table-2).

### Literature review

There are several case reports and case series about haemochromatosis<sup>2-3</sup> but majority of the reports are on male hypogonadism associated with haemochromatosis. Haemochromatosis occurs due to a defective control of iron absorption leading to excessive iron stores in the body. Surplus iron that is deposited in the organs lead to increased intracellular

iron leading to oxidative damage and impaired membrane dependent functions of organelles like mitochondria, microsomes and lysosomes<sup>4</sup>. Manifestations can range from simple fatigue to diabetes mellitus, hepatic failure, sexual dysfunction, infertility etc, depending on the site and extent of the iron deposit.

**Table 2 - Blood parameters**

Investigation	Values
Serum Ferritin	<b>2236ng/ml (15-200ng/mL)</b>
Serum Transferrin	211 mg/dL (212 -360mg/dL)
Serum iron	<b>262µg/dL (60-160µg/dL)</b>
TIBC	262µg/dL (250-460µg/dL)
C- peptide	0.368 ng/mL (0.9 -43ng/mL)
Ceruloplasmin	655 mg/L (250-430mg/L)
Hb	11.4gm% (12-16gm/dL)
HbA1c	10.7%(4.7 -8.5%)
Serum Magnesium	2.52 (1.5-2.4mg/dL)
Electrolytes	Na 135mEq/L (136-145mEq/L) K 4.3mEq/L (3.5-5mEq/L) HCO 28mEq/L (23-28mEq/L)
Serum FSH	<b>0.106 mIU/ml (5-20mIU/mL)</b>
LH	<b>0.208 mIU/ml (5-22 mIU/mL)</b>
TSH	1.699 mIU/ml (0.5 – 5mIU/mL)
FTC	1.12 µg/dL 4-11µg/dL
Prolactin	8.7 µg/L (<20 µg/L)
Cortisol	10.55 µg/dL (8-20µg/dL)
Mutation analysis for HFE,HFE2,HAMP in 6p22.1,1q21.1,9q13.1	<b>No mutations in direct sequencing</b>



**Fig 1 - MRI picture, GRE image showing lateral ventricles with hypointensity**



**Fig 2 - MRI Brain – GRE image showing hypointensity of Foramen of Luschka**

Haemochromatosis can be of two types Primary or Hereditary Haemochromatosis(HH) which is due to a HFE gene defect or a non-HFE mutation like haemojuvelin, Hecpudin, Transferrin receptor mutations. In secondary haemochromatosis the iron excess is due to conditions like congenital haemolytic anaemias, environmental and lifestyle factors.

Classical HH is more common in Europeans with a prevalence of 1/200. Reports from Asian continent has identified non HFE<sup>3,5</sup> gene defects.

Hereditary haemochromatosis usually presents in the third or fourth decade of life and usually is an incidental finding. It is more prevalent in male than in female(25:1)<sup>6</sup> Patients may present with a myriad of symptoms depending on the organ involved.

Unless there is high degree of suspicion the diagnosis of haemochromatosis is elusive. Apart from the clinical manifestations and family history, increased serum ferritin level and transferrin saturation of >45% will help in clinching the diagnosis. In early stages the ferritin levels may not be high and in Asian subjects, the co existing anaemia and iron deficiency or co existing thalassaemia may complicate the picture.

Among the imaging modalities, MRI is the most sensitive to pick up the haemosiderin deposits of the pituitary, pancreas. Dual energy CT is helpful in quantifying the deposits. A biopsy of the liver will show the evidence of iron deposits in the cells. Currently the availability of MRI has replaced the need for liver biopsies to diagnose haemochromatosis. Current recommendation for liver biopsy is to assess the hepatic fibrosis to prognosticate the patient outcome<sup>4</sup>. Early diagnosis and treatment has the potential to prevent damage to liver, heart and other organs. With treatment, total reversal of hypogonadism and return of normal sexual function and fertility in men have been reported<sup>7</sup>.

Reports on hypogonadism in women are few and majority are about late onset hypogonadism i.e. at fourth or fifth decade of life<sup>6</sup>.

Treatment is usually prolonged. Periodic venesections are performed to reduce the iron overload. This may take upto 24 months to bring down the serum Ferritin level to the recommended 50µg/l<sup>8</sup>. Later the level is maintained by venesections done at more infrequent intervals i.e. 2-3 months once. Chelating agents like Desferrioxamine is used in secondary haemochromatosis.

Modification in diet is advised to reduce the intake of iron. Patients are also encouraged to take chelating agents along with food (eg dairy products) to reduce the iron absorption.

Mutation analysis is important to map the gene defect in families and to offer counseling<sup>9</sup>. Even if the patient is cured and fertility concern is answered, it is important to monitor on a long term basis as the risk of hepatocellular carcinoma is high.

## Treatment in fertility clinic

Patients often present with sexual infantilism or infertility in both genders. Treatment to reduce iron overload and carefully tailored treatment with Testosterone supplements, hCG and gonadotropins will help improving libido, correcting erectile dysfunction and semen parameters in men.

In women, gonadotropin administration will help to induce ovulation and to achieve fertility. The addition of IUI or IVF to ovulation induction depends on the other co-existing causes of infertility.

Genetic counselling prior to treatment of infertility is a must. Prenatal mutation analysis is available but not commonly done<sup>8</sup>.

## Discussion

Our patient had certain unusual features which need to be explored further.

Presentation at the second decade as in this patient is not common in primary haemochromatosis. Reports on juvenile type HH discuss about the mutations in haemojuvelin gene (HFE2) and hepcidin gene (HAMP gene –HFE2B) presenting in second or third decade of life. Here both these mutations are not seen. Though the mutation analysis for TFR2 (Transferrin Receptor) and FPN1 (Ferroportin 1) have not been ruled out, the possibilities of these are very limited.

Her response to gonadotropins could be due to initial low dosage. But complete absence of response despite increasing the dosage to 150IU is intriguing. Whether the resistance to stimulation is directly related to the haemosiderin deposit in the ovary is unclear.

The take home message is that the primary diagnosis can be easily missed in any patient and it is advisable to involve multi disciplines. This goes a long way in not only treating their infertility but also improving their life expectancy.

Identification of regions with high incidence of haemochromatosis, gene mapping and maintaining a registry will enhance awareness and early diagnosis. Creating a support group will improve their coping up skills.

## Acknowledgement

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# Case Report

## Pemphigus Vulgaris following ART pregnancy

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### Abstract

Pemphigus vulgaris is a rare autoimmune disorder which affects the skin and mucous membrane. It affects both sexes equally. We had a patient who underwent ART treatment for infertility, affected by this disorder during treatment. Now she is in a dilemma to decide regarding the frozen embryos.

**Key Words:** Pemphigus vulgaris, Pregnancy, Infertility, Autoimmune, Acantholysis, ART, FET.

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### Introduction

The word "Pemphigus" is derived from the Greek word "Pempnix" which means bubble or blister<sup>1</sup>. It is a group of chronic bullous disease and was named by Wichman in 1791. Common in all races, but more common in Jews<sup>2</sup>. Pemphigus in India tends to occur at a younger age and is more severe compared to Western countries<sup>3</sup>. The incidence of pemphigus is 0.09 to 1.8%<sup>4,5</sup>. Pemphigus vulgaris is a rare autoimmune, intraepithelial disorder affecting skin and mucous membranes (Fig 1). It presents as large flaccid bullae on a normal or erythematous base which break easily.

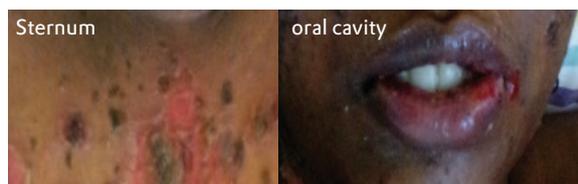


Fig 1 - Muco cutaneous lesions

They are mostly seen in oral mucosa, scalp, midface, sternum and groin<sup>6</sup>. In the oral cavity, the buccal mucosa and the hard palate are the commonest sites of involvement, followed by lips, tongue, floor of the mouth and gingiva in descending order of frequency<sup>3</sup>. It is mediated by circulating antibodies against keratinocyte cell surface. The auto antibodies target the proteins called desmogleins. The desmogleins are present in the outer layer of the skin.

### Case report

Mrs.X, 29 yrs, married to Mr.Y, 30 yrs presented with primary infertility for 2½ yrs. She attained spontaneous menarche at 12 yrs of age and continued to have irregular induced cycles mostly with progestogens. Coital history was normal. She was on oral contraceptive pills(OCP) for 6 months for cycle regularisation 3yrs ago. Subsequent to OCP intake she

had cerebral venous thrombosis(2008) diagnosed by MRI and had been treated with oral anticoagulants for 2 yrs. For fertility, she had attempted two cycles of Intra uterine insemination (IUI) elsewhere which failed. She underwent 3 cycles of IUI with clomiphene citrate 100mg and gonadotrophins, in our department which also failed.

As her multiple IUI attempts failed, she was planned for ART(August-2012) after clearance from Neurophysician. The protocol used was flare GnRH agonist protocol along with controlled ovarian hyperstimulation using highly purified urinary FSH. She had mild hyperstimulation and was monitored. Out of 26 oocytes obtained, the number of M II(mature) oocytes were 22. Intracytoplasmic sperm injection (ICSI) was done with husband's spermatozoa and 19 oocytes showed fertilization and all of them cleaved. Blastocyst transfer was done on D5 with 2 expanded blastocysts. The remaining 12 embryos, all blastocysts, were frozen. Micronised vaginal progestogens were given for luteal support and advised to do serum β hCG after 2 weeks to confirm pregnancy. It was a biochemical pregnancy and progestational support was stopped.



Fig 2 - Patient with muco cutaneous lesions in face, chest & scalp

After 4 months of ART/ICSI cycle, in Jan 2013 she underwent frozen embryo transfer (FET) after getting a neurophysician opinion regarding hormone

replacement treatment for FET. Programming of the endometrium was done with increasing doses of estradiol valerate and luteal support given with vaginal progestogens from D14 (29th Dec 2012) of menstrual cycle. Embryos were thawed and 3 expanded blastocysts with survival rate of 1-70%, 2-20% were transferred. Luteal support continued with estrogens and progestogens. She was advised to do serum  $\beta$  hCG on 16.01.13, which showed positive result.

This time again she achieved pregnancy but she developed bullous skin lesions 2 days after pregnancy confirmation and diagnosed as pemphigus vulgaris (Fig 2) on clinical examination. Nikolsky's sign was positive. She was given topical application and waited for ultrasound for confirmation of clinical pregnancy. Scan at 6 weeks confirmed a biochemical pregnancy. She discontinued progestogen. Then she was started on oral steroids and continued for 3 months. She temporarily stopped medications for one month as there was no formation of new lesions. But she had a relapse and developed blisters all over the body, turned into raw areas, developed painful oral ulcers, dysphagia and fever with chills. She was admitted for 20 days and treated with steroid infusion and immunosuppressant. Diagnosis was confirmed by histopathology with Tzanck smear. She was advised to take chronic steroid therapy. Hormones-estrogens and progestogens as one of the causative factor for PV was discussed with the couple by the dermatologist.

She was reviewed in our department in November 2013. Since progestogens were incriminated in the appearance of the skin lesions, patient was worried about further treatment.

#### Following options were discussed:

1. Repeat FET if she is permitted another HRT schedule
  2. Surrogacy with frozen embryos if pregnancy is not permitted for the patient.
- Currently she is on steroid infusion thrice a month, immunosuppressant and calcium.

## Discussion

Most of the autoimmune diseases occurs more frequently in women than in men and this is because of the possibility of influence of sex hormones over development of autoimmunity. During pregnancy, changes occur in the levels of estrogens and progesterones dramatically and also in cortisol, norepinephrine and dehydroepiandrosterone. This partially influences profound immunological changes throughout pregnancy and during postpartum period. These changes are very essential to accommodate the semiallogeneic fetus and include immunosuppressive and immunoregulatory processes<sup>6</sup>.

Pemphigus vulgaris is an autoimmune bullous dermatosis. Desmoglein 3 is found in desmosomes and auto antibodies are formed against it<sup>1</sup>. Apart from genetic factors, immunological factor is required to trigger pemphigus vulgaris. It also coexists in other autoimmune problems such as myasthenia gravis and lupus erythematosus<sup>6</sup>. The 3 primary subsets of pemphigus include pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus<sup>7</sup>.

Each type of Pemphigus has distinct clinical and immunopathologic features. Pemphigus vulgaris accounts for approximately 70% of pemphigus cases. PV if not treated is a life threatening disease. The mortality rate is 5-15%<sup>8</sup>. Secondary infection is the most common cause of death. As it is a lifelong disease, needs prolonged treatment. When steroids are started, improvement can be seen within few days. The oral blisters heal slowly. Further formation of blisters is stopped in 2-3 weeks. Complete healing however takes time<sup>9</sup>. Lifelong low dose medication is required for some. Diagnosis is by Tzanck smear preparation which is simple, rapid, patient friendly and non-invasive. Hence it can be used instead of immunofluorescence testing for early pemphigus<sup>10</sup>.

Because of its autoimmune nature like systemic lupus erythematosus, it gets precipitated or aggravated during pregnancy<sup>11</sup>. Our patient had flare-up of disease during the period of early pregnancy while on progestogens.

Apart from hormones, early pregnancy, stress can also trigger PV. This is a rare presentation of Pemphigus vulgaris which occurred due to hormones in a ART cycle.

**Acknowledgement:** Our sincere thanks to Dr. Sakthikandan, the treating dermatologist, for providing the pictures of the patients and Dr. N. Pandiyan for his guidance & Dr. Kanchana Devi for giving their suggestions during the preparation of this article.

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#### **Sir Robert Hutchison's Petition and the Medical Humanities**

From inability to let well alone  
From too much zeal for the new and contempt for what is old  
From putting knowledge before wisdom, science before art, and  
Cleverness before common sense;  
From treating patients as cases;  
And from making the cure of the disease  
More grievous than the endurance of the same,  
Good Lord, deliver us.

-Sir Robert Hutchison (1871- 1960)

# Case Report

## An Interesting Case of Thyroid Storm

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### Abstract

Thyroid storm is a rare complication of uncontrolled hyperthyroidism which has multisystem involvement and high mortality if untreated. We present a case of thyrotoxicosis progressing to thyroid storm which was precipitated by infection. The clinical presentation was confounded by the presence of underlying mitral regurgitation and atrial fibrillation.

**Key Words:** Hyperthyroidism, Thyrotoxicosis, Thyroid storm

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### Introduction

Thyroid crisis or thyroid storm, also known as accelerated hyperthyroidism is a medical emergency, which requires high index of suspicion and early, prompt and appropriate management in order to minimize mortality. Although the exact incidence is unknown, a Japanese study reported an estimated incidence of thyroid storm in all hospitalized patients in Japan to be 0.20 per 100,000 per year<sup>1</sup>. The overall incidence in hospitalized patients with overt hyperthyroidism is around 1 to 2%<sup>2,3</sup>.

Many criteria have been put forward for the diagnosis of thyroid storm, since it is predominantly a clinical diagnosis, and thyroid function tests may not be much different from those of uncomplicated hyperthyroidism. The presence of multisystem involvement including cardiovascular, gastrointestinal and neurological manifestations makes it challenging for the clinician to diagnose and treat this life threatening condition. When treatment is successful recovery usually occurs in one or two days.

### Case Report

A 44 year old lady presented with complaints of left sided chest pain, breathlessness and palpitations of three years duration, with associated loss of weight. She was known to have hyperthyroidism, for which she had been treated but had discontinued her medications for the past 6 months. She had also been diagnosed to have heart disease but details of treatment were not available.

On examination, she was thinly built, had pallor, glossitis and had a staring look. She also had a diffuse goitre. There was no pedal edema or enlarged lymph nodes. On examination of vital signs, she was found to have tachycardia, with irregularly irregular pulse of varying volume, and an apex pulse deficit of 15. Blood pressure was 100/70mmHg. Systemic examination

revealed an apical impulse which was shifted outward, with a pansystolic murmur of grade 3/6 in the mitral area. She also had a moderate splenomegaly. Neurological examination was normal except for fine tremors. With a clinical diagnosis of hyperthyroidism, with mitral regurgitation and atrial fibrillation, along with anemia and splenomegaly, laboratory investigations were carried out.

Investigations revealed a pancytopenia (Hb 5.8 mg/dl, Total WBC count 1900/cu.mm and platelet count of 62,000/cu.mm). Peripheral smear showed dimorphic anemia, with hypersegmented neutrophils, and thrombocytopenia. Thyroid function tests were suggestive of hyperthyroidism (Free T<sub>4</sub> 4.04ng/dL, TSH<0.01μIU/ mL). Other biochemical tests, including liver function, renal function and serum electrolyte estimations were normal. Serum vitamin B<sub>12</sub> level was done which was markedly decreased (39 ng/mL). ECG showed atrial fibrillation with fast ventricular rate and chest radiograph showed cardiomegaly. ECHO revealed moderate MR, TR, mild PAH, with dilated LA and RA. USG abdomen confirmed splenomegaly.

Therefore, she was diagnosed to have hyperthyroidism, with mitral regurgitation and atrial fibrillation, along with pancytopenia due to Vitamin B<sub>12</sub> deficiency. She was started on Vitamin B<sub>12</sub> supplementation 1000mcg/ day, along with propranolol 20mg twice daily. After a few days, her counts started improving, and hence carbimazole was initiated. However, later she showed a drop in her total WBC count, and carbimazole was subsequently withheld. While in the ward, she developed thrombophlebitis of the left forearm. This was followed by high grade fever, with a temperature of 104.6° F, associated with vomiting, loose stools, altered sensorium and jaundice. An initial diagnosis of infective endocarditis was considered, and patient was started on antibiotics after taking blood cultures. However, patient continued to worsen clinically and

biochemically. In the background of hyperthyroidism, fever with multisystem dysfunction not responding to antibiotics, neurological manifestations, and jaundice, a diagnosis of thyroid storm was considered. Since all other work up for fever was negative, Thyroid storm was a diagnosis of exclusion, based on the clinical features. Under cover of antibiotics she was started on intravenous hydrocortisone, along with Propyl Thiouracil (PTU) at a dose of 200mg 6th hourly. The patient showed remarkable improvement, and her fever subsided, sensorium improved and LFT returned to baseline. The patient was discharged with a final diagnosis of thyrotoxicosis leading to thyroid storm, with mitral regurgitation and atrial fibrillation, and pancytopenia secondary to Vitamin B12 deficiency.

## Discussion

Our patient was a known case of mitral regurgitation with atrial fibrillation, who also had uncontrolled hyperthyroidism. The treatment of hyperthyroidism was complicated by pancytopenia due to Vitamin B12 deficiency, which can be worsened by anti-thyroid medications. Further, the onset of fever with multisystem involvement posed a clinical challenge, as infective endocarditis and sepsis could also manifest in a similar fashion as accelerated hyperthyroidism. With a clinical diagnosis of thyroid storm, we treated the patient with antithyroid drugs, carefully monitoring her blood counts, and also with beta blockers, intravenous steroids and supportive measures such as hydration, antibiotics and antipyretics.

Thyroid storm, also referred to as thyrotoxic crisis, is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones in individuals with thyrotoxicosis. The presence of hyperthyroidism or thyrotoxicosis is a prerequisite for making a diagnosis of thyroid storm.

Clinical features are fever out of proportion to an apparent infection, sweating, tachycardia out of proportion to the fever, and gastrointestinal symptoms such as nausea, vomiting, diarrhoea and jaundice. As the storm progresses, symptoms of central nervous system dysfunction including increasing agitation and confusion, delirium, coma and rarely seizures. Cardiac manifestations in the form of tachycardia, hypertension, arrhythmias mainly supraventricular and atrial fibrillation, and pulmonary edema or high output cardiac failure are common<sup>4</sup>.

Thyroid crisis is a predominantly clinical diagnosis because the laboratory findings may not be much different than those of patients with uncomplicated hyperthyroidism. Treatment needs to be initiated urgently as the mortality rates of untreated thyroid storm reach 20 to 30%. It includes antithyroid drugs to reduce the hormone production, drugs to block the effect of already circulating excessive thyroid hormones, and finally management of systemic effects as well as control of triggering factors<sup>5</sup>. Thus, it may be treated with lugol's iodine, propyl thiouracil, propranolol and steroids. Additionally antibiotics if infection is present and other supportive measures such as cooling, oxygen, and intravenous fluids can be used.

## Conclusion

Thyroid storm is a life threatening emergency in patients with uncontrolled hyperthyroidism. Early clinical diagnosis, along with prompt initiation of multifaceted treatment will help in reducing mortality.

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# Case Report

## Unilateral Blaschkoid Lichen Planus - A Rare Presentation of a Common Dermatological Entity

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### Abstract

Lichen planus (Greek leichen, "tree moss"; Latin planus, "flat") is a unique, immunologic mediated inflammatory disorder, that affects skin, mucous membranes, nail & hair. It is a disease of unknown etiology and is characterized by purple, polygonal, pruritic, flat topped papules.

Linear lesions in lichen planus can be due to isomorphic phenomenon or due to mosaicism, where the lesion follow Blaschko`s lines. The latter are unique lines which may be followed by other conditions like epidermal nevi, psoriasis, lichen striatus, Darrier`s disease and porokeratosis to name a few<sup>2,3</sup>.

Here we report an interesting presentation of Blaschkoid lichen planus in association with atopy, in a 22 year old woman.

**Key Words:** Blaschko`s lines, Blaschkoid lichen planus, Unilateral lichen planus

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### Introduction

Lichen planus (LP) was first described by Erasmus Wilson in 1869. It is characterized by purple, polygonal, pruritic, papular eruption of unknown etiology affecting skin, mucous membranes and the nails<sup>1</sup>.

It can range from the generalized form to the much localized form. Less commonly, the skin lesion in lichen planus may have a linear arrangement. This may be due to trauma (Koebner phenomenon) or due to their tendency to follow the lines of Blaschko. The latter is known as Blaschkoid lichen planus, and is seen in only 0.5% of patients<sup>2</sup>.

### Case report

A 22 year old lady presented with complaints of itchy raised skin lesions over her left upper chest, upper arm and the second webspace, over the past two months. There was no history of preceding trauma at the site of the lesions. She gave a history of similar lesions when she was around 10 years of age. The lesions had first appeared over the medial aspect of her left upper arm and left side of chest and subsided two months after the onset. At present, she complained of recurrence of lesions at the same sites over the past two months [Fig 1,2,3]. She was completely asymptomatic between the two episodes.

### Past History

There was past history of Varicella zoster, one year back but she recovered without any dermatological sequelae. She had a history of allergic rhinitis. There was no past history of jaundice or history of any dental procedures. She was not on any chronic medication.



**Fig 1** - Well defined multiple violaceous flat topped papules, reticulate plaques with minimal scales and hyperpigmented atrophic macules observed over the medial aspect of (L) upper arm. Intervening areas show normal skin.



**Fig 2** - Similar multiple well defined violaceous flat topped papules with minimal scaling observed over the (L) upper chest over 2nd intercostal space



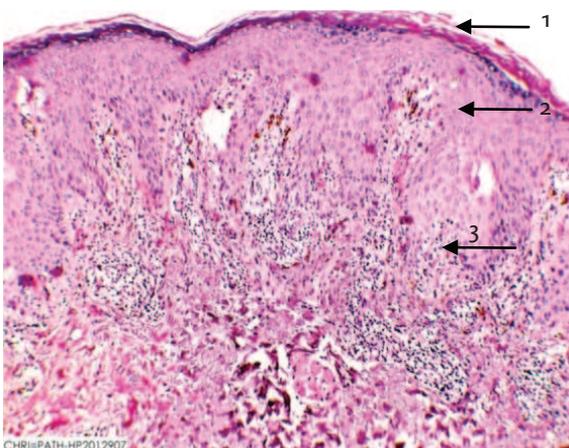
**Fig 3** - Flat topped papules with minimal scaling observed over the interdigital space between the (L) index finger and middle finger.

With the above clinical findings, the following differential diagnoses were considered :-

- Linear Lichen Planus
- Lichen Striatus
- Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)
- Blaschkoid Lichen Planus

Routine blood investigations, urine routine, liver and kidney function tests were within normal limits. Serology for HIV and VDRL were non-reactive. HBsAg and HCV were negative.

Four millimeter punch biopsy was taken from the papule on the medial aspect of left upper arm and sent for histopathology. It revealed hyperkeratotic epidermis with hypergranulosis, acanthosis and basal cell vacuolation with melanin incontinence. Dermis showed Civatte bodies with Max Joseph space. Dense band like lymphocytic infiltrate in papillary dermis with melanophages was noted (Fig 4).



**Fig 4** - Histopathology showing hyperkeratotic epidermis (1) hypergranulosis (2) acanthosis and basal cell vacuolation. Dense band like lymphocytic infiltrate (3) in papillary dermis with melanophages noted.

With the above clinical and histopathological correlation, the diagnosis of Unilateral Blaschkoid Lichen Planus was arrived at.

She was managed with Topical corticosteroid (0.1% Mometasone), oral antihistamines (T.hydroxyzine 10mg) and liquid paraffin for topical application for one month.

On follow up, the lesions regressed leaving a post inflammatory hyperpigmentation.

## Discussion

The lines of Blaschko were first described and drawn by Alfred Blaschko, in 1901<sup>3</sup>. In contrast to dermatomes, these lines form a V-shape over the spine, an S-shape on the lateral and anterior aspect of the trunk, and an inverted U-shape from the breast area onto the upper arm. On the extremities, they follow a perpendicular direction and on the abdomen, they form whorls<sup>4</sup>.

The embryological basis of distribution pattern of these lines is so far an enigma<sup>2</sup>. Blaschko lines represent a form of 'mosaicism', where two or more genetically distinct cell populations are present in an individual derived from a single zygote<sup>2,3</sup>. Blaschko's lines do not correspond to any known nervous, vascular or lymphatic structures<sup>5</sup>. These lines represent distribution of autonomic motor-visceral afferents or stretching of the skin during embryogenesis. The lines of Blaschko may be followed by certain X-linked, congenital and inflammatory skin disorders<sup>6,7</sup>.

The course of Blaschkoid LP is usually benign and self-limiting<sup>8</sup>. Dermatoses which may be confused with this type of lichen planus are those that present linearly or follow the lines of Blaschko like nevi, psoriasis, lichen striatus, Darrier`s disease and those dermatoses which have a dermatomal distribution like Herpes zoster<sup>9, 10</sup>.

The features in favour of a true Blaschkoid lichen planus in this patient were the absence of preceding trauma or illnesses, characteristic clinical morphology and histopathology. Other interesting findings that were observed were the unilateral distribution of the lesions and the association with atopy.

## Conclusion

This case of Blaschkoid lichen planus is reported for its uniqueness and rarity with regard to its unilateral distribution and its association with atopy.

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#### Tale of Two Cities

It was the best of times, it was the worst of times,  
It was the age of wisdom, it was the age of foolishness,  
It was the epoch of belief, it was the epoch of incredulity,  
It was the season of light, it was the season of darkness,  
It was the spring of hope, it was the winter of despair,  
We had everything before us, we had nothing before us,  
We were all going direct to Heaven, we were all going direct the other way-  
In short, the period was so far like the present period.

- Charles Dickens

## Case Report

### Wide Resection and Reconstruction with Nonvascular Fibular Autograft in the Treatment of Giant Cell Tumour (GCT) Distal end of Radius

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#### Abstract

Giant cell tumour (GCT) of distal radius follows a comparatively aggressive behaviour. Wide excision is the management of choice, but this creates a defect at the distal end of radius. The preferred modalities for reconstruction of such a defect include vascularized/non-vascularized bone graft, osteoarticular allografts and custom-made prosthesis. We here present our experience with wide resection and non-vascularised autogenous fibular grafting for Giant Cell Tumour of distal radius.

**Key Words:** Giant Cell Tumour, Wide Resection, Fibular Graft.

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#### Introduction

Giant cell tumours (GCT) are malignant and aggressive lesions with variable clinical manifestation. Treatment of GCT of bone is by curettage and adjuvant therapy to eliminate the remnant<sup>1</sup>. Bone graft or methylmetacrylate is used to reconstruct the resulting bone defect. But the treatment of Stage III GCT remains controversial<sup>2</sup>, i.e., to carry out en-bloc resection or intralesional. However, the functional deficit following the surgical procedure for a giant cell tumour of distal end radius should be weighed with the chances of recurrence<sup>3,4</sup>.

The tumour has to be completely excised in order to obtain better chance of cure but would result in compromising the articular surface, which may lead to complex and sometimes repeated reconstructive procedures. Reconstruction by Proximal fibular autograft (vascularised and non-vascularised) has been used with good results.

#### Case Report

A 42 year old women, a housewife presented to the Department of Orthopaedics, Chettinad Hospital and Research Institute with pain & swelling of her left wrist (Fig 1) of 6 months duration. There was a diffuse swelling of wrist more pronounced dorsally with painful restriction of wrist movements. X-ray and MRI revealed Campanacci grade 3 GCT of distal radius (Fig 2 & 3).

Cortical breach of the tumour is assessed by using Campanacci's<sup>5</sup> staging system. FNAC of the lesion revealed sheets of osteoclast type giant cells and moderate cytoplasmic stromal cells.

Wide resection and reconstruction with ipsilateral nonvascular fibular graft was done using dorso-radial

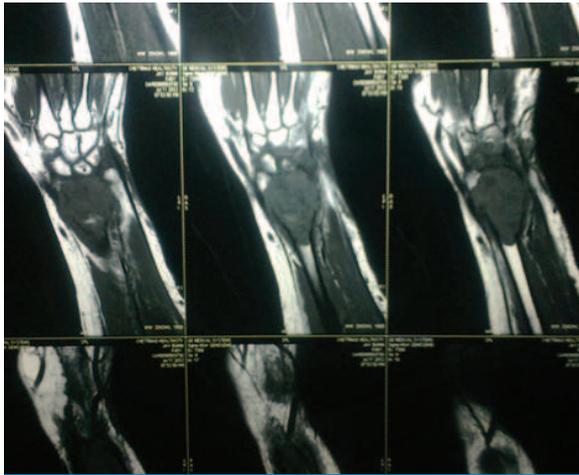
approach (Fig 4a & 4b). Grafted fibula was stabilised to the radius with a Dynamic Compression Plate and the fibulo-ulnar joint was stabilised with a K-wire (Fig 5a & 5b). Cancellous graft harvested from proximal tibia was placed at radio-fibular junction. Postoperatively, wrist splint and physiotherapy were given.



**Fig 1 - Swelling of the left wrist**



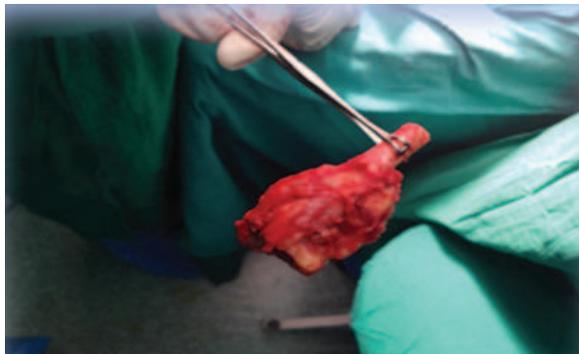
**Fig 2 - X-ray of the left wrist showing tumour distal end of radius with characteristic soap bubble appearance.**



**Fig 3** - MRI-left wrist showing Expansile Lytic lesion in the distal end of radius.



**Fig 4a** - Intraoperative picture of left wrist showing the defect after excised distal end of radius.



**Fig4b** - Resected distal end of radius along with the tumour.



**Fig 5a** - Post operative x-ray showing reconstructed distal radius with non vascularised proximal fibular graft.



**Fig 5b** - Post operative X-ray showing resected proximal fibular.

### Results

At 15 months post-operatively, patient had painfree Left wrist dorsiflexion of 70 degrees, palmar flexion of 70 degrees (figure 6a&b) and a reasonably good rotation of forearm. She is able to perform her day to day activities comfortably. On X-ray fibula-radial junction had healed well and there were no graft related complications or tumour recurrence.



**Fig 6a** - Dorsiflexion of left wrist at 15 months postoperative period.



**Fig 6b** - Palmar flexion of left wrist at 15 months post operative period.

### Discussion

Giant cell tumour is a lesion with higher rate of recurrence<sup>3</sup>. Functional deficit following the surgical procedure for a giant cell tumour of distal end radius should be weighed with the chances of recurrence<sup>4</sup>.

Thorough curettage of the tumour with bone graft for the subsequent defect is accepted only if the tumour is histologically typical (tumours that are within the intact cortex).

Curettage and bone grafting for atypical and aggressive tumours would result in collapse of the articulating surface and recurrence of the tumour, which is avoided by performing en-bloc resection with reconstruction of distal radius. En-bloc resection is strongly recommended, especially in high grade tumours and those which have recurred, have pathological fracture, have enlarged rapidly or are frankly malignant.

Reconstruction<sup>6,7,8,9</sup> is mandatory after resection of the tumour to maintain the function and alignment. Various techniques for reconstruction includes iliac crest bone graft, distal radial allograft, centralisation of ulna, prosthesis and vascularised or non-vascularised fibular graft and prosthesis.

Proximal fibular<sup>10</sup> graft is reasonably congruous with distal radius. Its incorporation as an autograft is more rapid and predictable. Moreover, there is no significant donor site morbidity, easily accessible and the functional outcome is acceptable.

## Conclusion

Although the range of movements in the operated wrist is lesser than that of non-operated, but this surgical procedure yields a satisfactory functional outcome assuring the return of patients to their previous activities. Hence wide resection and reconstruction with non-vascular fibular autograft is a reasonable treatment option for Giant Cell Tumour – Distal End of Radius.

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### Answer to : Diagnose the condition

The ECG is characteristic of Apical hypertrophic cardiomyopathy (AHCM), a variant of Hypertrophic cardiomyopathy, commonly seen in Asian HCM patients. It shows very high amplitude (>12 large squares) R wave with giant T wave (>0.1 mV) inversion suggesting repolarisation abnormalities. The most impressive consistent changes in AHCM appear to be the enormity of the amplitude of the QRS complexes, mainly the R waves of the precordial leads, particularly V<sub>4</sub> and the rightward posterior and superior axis of the T waves. Echocardiogram revealed hypertrophy of the septal, anterior and posterior walls, but the apical hypertrophy was more severe.

- Dr.M.Chokkalingam, Consultant Cardiology, CSSH.

# Case Report

## Acquired Hemophilia with Hypopituitarism

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Both the authors \* & \*\* have contributed equally to the article.

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### Abstract

Acquired haemophilia is a rare haemorrhagic disorder which can present with mild to severe bleeding and can be potentially life threatening. Diagnosis of acquired haemophilia can be difficult because of the rarity of its presentation. It has been found to be associated with pregnancy, inflammatory bowel disease, hepatitis B and C, hypothyroidism and autoimmune disorders. We present the case of a 45 year old female patient with gum bleeding for two weeks with no family or personal history of a bleeding disorder. Further laboratory and radiological evaluation revealed a rare association of acquired haemophilia with hypopituitarism. Association of acquired haemophilia with hypothyroidism although by itself rare, is a known one, but acquired haemophilia with hypopituitarism (empty sella) is a rare one.

**Key Words:** Hypopituitarism, Acquired haemophilia, Coagulopathy, Empty sella, Prolonged aPTT.

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### Introduction

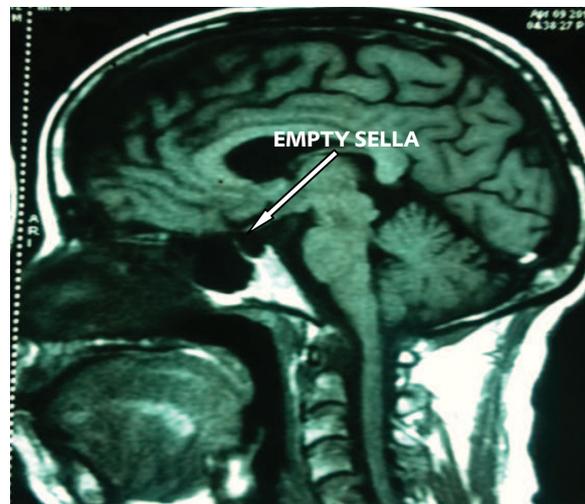
Hypopituitarism is a partial or complete insufficiency of one or more anterior pituitary hormones which can be congenital or acquired. The prevalence of hypopituitarism was 46 cases per 1,00,000 individuals<sup>1</sup> which is most commonly associated with conditions such as postpartum pituitary necrosis (Sheehan's syndrome), radiation, post trauma, autoimmune hypophysitis and empty sella. Acquired hypopituitarism is associated with combined hormonal deficiencies like growth hormone, thyroid, cortisol, follicle stimulating hormone and leutinizing hormone. Although it is known that hypothyroid patients may have a decrease in von willibrand factor and Factor VIII levels<sup>2</sup>, there are limited reports of hypopituitarism associated with factor VIII deficiency<sup>3</sup>.

### Case Report

A 45 yr old female patient, a known type II diabetic for 3 years was admitted with a history of spontaneous gum bleeding of 2 weeks duration with no similar previous episodes. There was no history of any other bleeding manifestations. She had no significant menstrual disturbances and her obstetric history was uneventful except for one spontaneous abortion in between the two normal deliveries. There was no bleeding disorder in the family. Patient is a betel nut chewer.

On examination, the patient was pale and with features of hypothyroidism. Patient had a poor oral hygiene with bleeding gums. Her vitals were normal. Examination of other systems did not reveal any abnormality.

Her haemoglobin was 5.6% and RBC 1.1 millions/cu.mm with normal leukocyte count and platelet count and peripheral smear revealed microcytic hypochromic anaemia. Her stool was negative for occult blood. Her creatinine was 1.4/dl, blood urea nitrogen of 22, sodium-129meq/L, potassium 3.6meq/L with fasting and posts prandial blood sugars, liver function tests normal. Thyroid functions confirmed a central cause for hypothyroidism (3-1.30pg/ml (2.5-3.9 pg/ml) 4-0.13ng/dl (.58-1.64ng/dl), TSH-3.03uiu/ml (0.34-4.6uiu/ml). Her viral markers for hepatitis were negative. The bleeding time, clotting time and coagulation profile were normal except for prolonged aPTT (29.2/23sec)



**Fig1** – MRI : Empty sella with compressed and atrophied pituitary

MRI brain (Fig 1) was done to assess for the central cause of hypothyroidism which revealed a hematoma in the maxillary sinus and an empty sella with compressed and atrophied pituitary stalk. Serum cortisol levels at baseline (7.49) were compared with levels after insulin induced hypoglycaemic test (10.6). This confirms the presence of hypopituitarism. She was transfused 3 units of blood for anaemia. But bleeding persisted and repeat aPTT values after 5 days revealed a non coagulable serum and hence 2 units of cryoprecipitate was transfused. Repeat aPTT values were 28.5/24.9 (Test/Control).

Since the patient with no previous history of bleeding and isolated prolongation of aPTT, improved after 2 units of cryoprecipitate, clinically the diagnosis of acquired haemophilia was considered with von willibrands disease a close FVIII levels-35% (Normal 50-150%), normal VWF levels (>240), and ANA-negative. Mixing studies were done to distinguish between factor deficiency and presence of inhibitors to VIII. It showed prolongation of aPTT after 2hrs of incubation which confirmed the presence of inhibitors. Further confirmation requires FVIII inhibitor levels which is available only in specialized labs and hence could not be done. Thus the diagnosis of acquired haemophilia associated with hypopituitarism was made. Patient was treated with prednisone-60mg then slowly tapered to a dose of 10mg/day along with thyroxine 100 µg/day. At follow up, aPTT levels normalised after a period of 3 months and mild ooze present occasionally.

## Discussion

Acquired haemophilia is a rare but potentially life threatening bleeding disorder with an incidence of 0.2-1 case per million per year<sup>4</sup> caused by the development of autoantibodies against plasma coagulation factors. Inhibitors to factor VIII is the most commonly observed abnormality and it may be associated with autoimmune disorders, pregnancy, inflammatory bowel disease, diabetes, hepatitis B and C, hypothyroidism and malignancies<sup>4</sup>. Few case reports show association with hypopituitarism<sup>3</sup>.

Clinically patients present with acute or recent onset, persistent soft tissue or mucosal or muscle bleeds<sup>5</sup> and rarely cerebral haemorrhage and an isolated prolongation of aPTT as opposed to patients with congenital haemophilia who present early in life and have major bleeds into joints. Both can be differentiated using mixing studies<sup>6</sup>. Though not all patients present with typical symptoms of severe bleeding or aPTT prolongation, the diagnosis of acquired haemophilia should be considered and investigated properly. FVIII levels and FVIII inhibitors assay (Bethesda Assay) are the confirmatory tests.

Tests to assess the etiology includes, assay of various anterior pituitary hormones at baseline and after stimulation ( Insulin Induced Hypoglycaemic test and ACTH stimulation test) which establishes the diagnosis of Hypopituitarism. Imaging studies will aid in confirming the diagnosis.

The treatment goals include -

1. control of bleeding episodes
2. eradicate inhibitors with immunosuppressive agents
3. treat the underlying disease

The treatment option for persistent mild bleeding includes factor VIII concentrates and/or desmopressin<sup>7</sup>. For major bleeding episodes and high inhibitors titres Activated protein complex concentrate (APCC), Factor VIII bypassing agents (FEIBA) and recombinant activated Factor VII (FVIIa) are used. Other strategies to control bleeding are to remove the inhibitors with plasmapheresis and immunoadsorption of the inhibitors to staphylococcal protein A or polyclonal sheep antibodies<sup>8</sup>. For eradication of the inhibitors, treatment was initiated with prednisone (1mg/kg/day) and cyclophosphamide (1.5-2 mg/kg/day) for a period of 5 weeks. Rituximab (anti CD-20) has recently shown effective eradication of the inhibitors as a second line of therapy<sup>9</sup>. Adequate replacement of the defective pituitary hormones<sup>1</sup> is the mainstay of therapy. Appropriate thyroxine replacements and steroids has shown to improve the factor VIII levels and decrease bleeding as in our case.

## Conclusion

Thus a rare association of acquired haemophilia with hypopituitarism is established. Diagnosis of this rare disorder should be considered in patients with unexplained persistent and profound bleeding from soft tissues and mucosa, with a prolonged aPTT and signs of pituitary hormonal deficiency. Prompt identification and treatment of the underlying condition is of utmost importance to avert a potentially life threatening bleeding.

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### திருக்குறள் 948

நோய்நாடி நோய்முதல் நாடி அதுதணிக்கும்  
வாய்நாடி வாய்ப்பச் செயல்

மு.வ உரை:

நோய் இன்னதென்று ஆராய்ந்து, நோயின் காரணம் ஆராய்ந்து, அதைத் தணிக்கும் வழியையும் ஆராய்ந்து, உடலுக்கு பொருந்தும் படியாகச் செய்யவேண்டும்.

**Couplet 948**

Disease, its cause, what may abate the ill: Let the physician examine these, then use his skill.

**Explanation**

Let the physician enquire into the nature of the disease, its cause and its method of cure and treat it faithfully according to medical rule.

# Case Report

## Pseudocholinesterase Deficiency Causing Delayed Recovery Following Caesarean Section in a Patient with Antithrombin III Deficiency

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**Key Words:** Pseudocholinesterase deficiency, Succinylcholine, Antithrombin III deficiency, Pregnancy

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### Introduction

Pseudocholinesterase deficiency can result in impairment of the metabolism of neuromuscular blocking agents like succinylcholine and mivacurium. We report the case of a 33 year old patient with known antithrombin III deficiency who underwent caesarean section under general anesthesia following which she had delayed recovery from anaesthesia, due to pseudocholinesterase deficiency.

### Case report

A 33-year-old lady, with known antithrombin III deficiency, on anticoagulants at 37 weeks of gestation was planned for Caesarean section as an elective procedure. She had a previous normal delivery 5 years ago. However on 40th post partum day, she had an episode of seizures for which CT scan brain was done which revealed transverse and sigmoid sinus thrombosis with venous infarct in left posterior temporal area. Haematological investigations revealed thrombocytopenia. She was started on warfarin and phenytoin which was continued for 1 year. She was on regular follow up with the haematologist since then. She was under regular antenatal checkup during her present pregnancy with constant followup by haematologist. The values of anticardiolipin antibody, lupus anticoagulant, protein C and protein S were normal.

At 30 weeks of gestation there was mild reduction in antithrombin III 81.8% (normal value 83-128) which further reduced to 66.1%. She was started on low molecular weight heparin (Enoxaparin 0.6 ml s/c OD). She was planned for elective caesarean section at 37 weeks of gestation. Routine preanesthetic assessment was done and all haematological and biochemistry lab values were normal except platelet count of 80000/mm<sup>3</sup>. Low molecular weight heparin was changed to unfractionated heparin 5000 Units IV qid on the previous day of surgery and stopped 6 hours before surgery. On the day of surgery platelet count - 61000/mm<sup>3</sup> PT - 12.6 (C), 13.5 (T), INR - 1.07, aPTT - 28 (C), 29.6 (T), Hb 11.7 g%.

In view of antithrombin III deficiency and thrombocytopenia it was decided to perform LSCS under general

anaesthesia. Patient was shifted to the operating room and her baseline hemodynamic parameters like heart rate, ECG, NIBP, oxygen saturation were noted. Anesthesia was induced with Thiopentone 250 mg iv and endotracheal intubation was facilitated with 7 mm ID cuffed endotracheal tube with succinylcholine 100 mg as a neuromuscular blocking agent. Intermittent positive pressure ventilation was initiated (Tidal volume - 450 ml, rate - 12, I:E ratio - 1:2) and surgery was started. 10 minutes after Succinylcholine, iv Atracurium 15 mg was given to facilitate adequate surgical relaxation and to prevent any increase in intracranial pressure (as the patient had previous history of cerebral venous thrombosis) consequent to coughing/bucking. A live male baby was delivered (APGAR at 1 minute - 8/10, at 5 minutes - 9/10). Following delivery of the baby, fentanyl 75 mcg, was given intravenously and infusion of oxytocin (20 units) was started. Anesthesia was maintained with isoflurane (0.6-0.8%) in oxygen:air (50:50). One unit of platelet was transfused intraoperatively. Patient was haemodynamically stable throughout the intraoperative period.

Anesthesia was reversed with glycopyrrolate 0.5 mg and neostigmine 2.5 mg when she developed spontaneous respiratory efforts (30 minutes after atracurium). However the respiratory efforts were not adequate. Hence a repeat dose of glycopyrrolate 0.2 mg and neostigmine 1 mg were administered. Respiratory efforts were still not adequate. Patient was drowsy, opening eyes to commands. Muscle power in all four limbs was grade 0-1. Ventilation was continued with 100% oxygen. Arterial blood gas sample revealed metabolic acidosis (pH-7.275, HCO<sub>3</sub><sup>-</sup> 18.6 mmol/L) potassium was 4.5 meq/l and ionised calcium was 0.98. 10% Calcium gluconate 10 ml given slowly over 15 minutes. Naloxone 200 mcg was given suspecting prolonged opioid effect. Muscle power and respiratory efforts were still poor and assisted ventilation was continued. Neuromuscular monitoring was instituted which showed TOF of 10%. Temperature was normal. Blood glucose was 108mg/dl. Pupils were equal B/L and reacting to light.

Two hours later, the muscle power improved to grade 4 and respiratory efforts were adequate. Repeat arterial blood gas sample showed pH-7.352, PO<sub>2</sub>-104, PCO<sub>2</sub>-33.8, HCO<sub>3</sub> - 18.2. Patient was conscious, obeying commands, respiratory efforts were good, with adequate tidal volume and oxygen saturation maintained 100 % with room air, TOF value of 90% and hence trachea was extubated. Muscle power in upper limb was grade-4 and lower limb was grade-2. Patient was then shifted to ICU in a hemodynamically stable condition for postoperative monitoring. Five hours after extubation patient was fully awake, oriented with normal motor power (Grade 5) in all limbs with-out any sensory deficit. Venous doppler of lower limbs showed no evidence of venous thrombosis. Heparin was restarted at 5000 U s/c tds, 6 hours after surgery. Post operative calcium (total) was 8.3 mg/dl, and magnesium 2.0 mg/dl. Platelet was 96000 lac/mm<sup>3</sup>.

The cause of delayed recovery from anesthesia was suspected to be either due to hypothyroidism or pseudocholine esterase deficiency which was evaluated post operatively.

Thyroid function test (free T<sub>3</sub>, free T<sub>4</sub> and TSH) were normal. 24 hours later she was started on warfarin 2 mg which was titrated according to PT and INR values. Heparin continued for 48 hours following surgery, after which she was on warfarin alone. She had an uneventful postoperative pe-riod and was discharged on the 8th postoperative day.

Pseudocholinesterase value was 258 U/L ( Normal lab reference was 2710-11510) which confirmed the cause for delayed recovery from general anaesthesia as pseudo choline esterase deficiency.

## Discussion

This case report summaries the perioperative events of a gravid patient with previously undiagnosed pseudocholinesterase deficiency and administration of succinylcholine. A pseudocholinesterase enzyme deficiency was suspected after failure to recover from the neuromuscular effect of the drug and the subsequent laboratory testing confirmed a pseudocholinesterase deficiency. Following intravenous administration of succinylcholine, about 90% of the total dose is hydrolysed by pseudocholinesterase ( into succinyl monocholine and choline ) within 1 min and only the remaining drug reaches the nerve-muscle junctions to bind with the receptor to result in the nerve end plate depolarization<sup>1</sup>. Two patients with severe pseudocholinesterase deficiency may develop apnea lasting 70–120 min after receiving a depolarizing agent<sup>3</sup>. The deficiency or abnormal enzyme can be either inherited or acquired. Acquired factors that decrease the pseudocholinesterase levels includes pregnancy, advanced liver disease, malnutrition, myxoedema, cancers, acute systemic infection and drugs (amitriptyline, neostigmine, pyridostigmine, chlorpromazine, cyclophosphamide, pancuronium, organophosphorus insecticides)<sup>4-6</sup>. Viby-Mogensen proposed that apnea is only moderately prolonged with as much as a 70% depression in pseudocholinesterase activity. Thus the

apnea is significantly prolonged only with extreme lower levels of pseudocholinesterase activity<sup>7</sup>. The deficiency or abnormal enzyme cannot be identified unless its has been tested specifically for, unless the individual experiences a prolonged effect of the drugs that are metabolised with pseudocholinesterase. The decreased enzyme activity can be due to deficient amount of normal enzyme (quantitative) or presence of abnormal enzyme (qualitative) or both. The adequacy of the pseudocholinesterase is determined qualitatively by the dibucaine number and quantitatively (pseudocholinesterase level) in units per liter<sup>7</sup>. Quantitative analysis of plasma levels of pseudocholinesterase is done using quantitative slab gel electrophoresis procedure. In our patient, the quantitative value of pseudocholinesterase level is 258 (Normal lab reference was 2710-11510). The amount of pseudocholinesterase activity is determined by colorimetric assay using benzylcholine substrate. Pseudocholinesterase levels less than 320 U/L are usually seen in individuals who are homozygous for atypical genes. The activity of plasma cholinesterase is measured by adding plasma to benzylcholine and observing the reaction spectrophotometrically. In persons showing succinylcholine sensitivity, the hydrolysis of the benzylcholine substrate was inhibited less by the local anaesthetic dibucaine than in persons with a normal response to succinylcholine and the dibucaine number refers to the percentage of inhibition, which is constant for a person independent of the concentration of the enzyme. The abnormal enzyme has only about 1/200 the affinity for dibucaine than the normal pseudocholinesterase. Dibucaine number is proportional to the function of pseudocholinesterase and is independent of the amount of the enzyme. It does not measure the enzyme concentration in plasma or the efficiency of the enzyme itself<sup>8-10</sup>.

Pregnancy is associated with 25% to 30% decreased pseudocholinesterase activity from the 10th week of gestation<sup>11</sup>. The enzyme level returns to non pregnant levels around sixth week postpartum. This in general is clinically not significant, as it takes about 70 % depression in the enzyme activity to cause a prolonged blockade after succinylcholine. There was no case report available to support the idea that in our patient, the decrease in pseudocholinesterase level was purely due to pregnancy status.

Ventilatory support remains the mainstay in managing the patient with pseudocholinesterase deficiency patients with prolonged apnea. In case of prolonged apnea following intravenous succinyl choline, administration of highly purified human serum Pseudocholinesterase decreases the duration of the induced apnea<sup>7</sup>. Investigating the other causes of prolonged apnea or recovery from anaesthesia helps in ruling out pseudocholinesterase deficiency. Our patient recovered completely with assisted ventilation alone, without the administration of acetylcholinesterases.

## Conclusion

Deficiency of pseudocholinesterase, either inherited or acquired, can have unexpected results regarding the patient's ability to metabolize certain drugs. This case

report described a 33-year old woman who developed apnea from prolonged neuromuscular blockade because of a decreased pseudocholinesterase value of 258 U/L. Individuals who are not diagnosed of this condition earlier pose a great challenge to anaesthesiologists because of the unexpected duration of action of succinylcholine. Implementing proper monitoring techniques such as peripheral nerve stimulator helps in differentiating pseudocholinesterase deficiency from other causes of delayed neuromuscular recovery.

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### Making faces at smoking mom!

The current technology allows us to view what we could not have visualised before – the reactions of an unborn to the obnoxious habits of its mom. That habit is of course smoking. In a new study carried out in Durham University, the researchers observed 4-D scans of the facial expressions of 20 fetuses of both smoking and non-smoking would-be moms. These observations were done 4 times between 24 and 36 weeks of pregnancy. The fetuses of the smoking moms showed higher rates of mouth movement and greater frequency of facial touching compared to the fetuses of non-smoking women. The authors feel that these reactions could be due to the effect of smoking on the development of foetal nervous system. However, all the babies were born healthy. The study is published in the latest issue of *Acta Paediatrica*.

[<http://www.medicinenet.com/script/main/art.asp?articlekey=187616>]

- Dr. K. Ramesh Rao

# Case Report

## Ropivacaine Induced Seizures

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**Key Words:** Ropivacaine, Seizures, Toxicity

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### Introduction

Ropivacaine- a relatively new long acting local anaesthetic agent is a pure S-enantiomer. Local anesthetic toxicity commonly affects the cardiovascular and central nervous systems (CNS), with CNS symptoms being more diverse varying from numbness of tongue, visual disturbance and muscular twitching to more serious manifestations like convulsions, coma, respiratory arrest, and cardiovascular arrest. Brachial plexus block is a frequently used technique for upper limb procedures and is more desirable to use a longer acting local anesthetic for the same. Among the long acting local anaesthetics, ropivacaine is less toxic compared to bupivacaine with only few cases of cardiac or central nervous system toxicity being reported. We report a case of generalised tonic clonic seizure (GTCS) that occurred in a patient during administration of ropivacaine for brachial plexus block.

### Case Details

A 35-year-old male (65 kg, 160 cm) was scheduled for open reduction and internal fixation of fracture of right radius and ulna. He had no significant medical or surgical history and also was not allergic to any drugs or food. All the blood investigations were within normal limits. In the operation theatre standard monitoring of

electrocardiograph, oxygen saturation and non invasive blood pressure was instituted. Peripheral venous access was established and IV midazolam 2 mg was given.

Under strict aseptic precaution, after infiltrating skin with 2% lignocaine, nerve stimulator guided brachial plexus block was performed. After confirming negative aspiration of blood, 35 ml of 0.4% (150 mg in 35 ml) ropivacaine was injected over 10 minutes.

Patient was responding to commands during administration of ropivacaine. However after 20 ml of administration of drug, patient had generalized tonic clonic seizures, during which heart rate increased from 75/min to 90/min and NIBP increased from 126/78 mm Hg to 144/84 mm Hg. Immediately administration of ropivacaine was stopped, 100% oxygen was administered, midazolam 3mg was given and general anaesthesia was induced with thiopentone 250 mg, fentanyl 100 mcg, succinylcholine 100 mg and trachea was intubated. Seizures stopped after induction of general anaesthesia and maintained with O<sub>2</sub>:air at 1:1 and isoflurane at 1.2 MAC with ivatracurium bolus doses.

**Table 1** - Cases of adverse effects with Ropivacaine after regional anaesthesia with the technique and dosage used; ND-not determined(3-8)(Concise of all case reports)

Regional Anaesthetic Technique	Amount of Ropivacaine injected	Plasma Concentration	CNS effects	CVS effects
Epidural	2.0 mg/kg	ND	GTCS	Tachycardia
Epidural	0.5 mg/kg	1.4 mg/litre	GTCS	None
Brachial Plexus Block	300 mg	2.7 mg/litre	GTCS	None
Brachial Plexus Block	4.5 mg/kg	2.0-4.0 mg/litre	Oral Numbness	Tachycardia and Hypertension
Sciatic Block	2.5 mg/kg	1.6-3.6 mg/litre	GTCS	Bradycardia
Interscalene Block	6 mg/kg	4.0-6.0 mg/litre	Oral Numbness	Tachycardia
Interscalene Block	2.3 mg/kg	ND	GTCS	None

There were no cardiovascular changes observed in ECG except sinus tachycardia. Patient was observed for next 30 minutes and after ruling out other causes of generalized tonic clonic seizures like hypoxemia, hypercarbia, hypoglycemia, electrolyte abnormality and acidosis, surgery was commenced under general anaesthesia. Intra operative period was uneventful and surgery lasted for 170 minutes. After neuromuscular antagonism, patient's trachea was extubated uneventfully. Effect of brachial plexus block lasted for 240 minutes, with no further episodes of seizures and complications for the next 24 hours. Patient was discharged after 7 days of uneventful postoperative period.

Though ropivacaine has been used extensively in brachial plexus block and other regional anesthesia techniques, only a few reports of ropivacaine induced seizures are available. In all these cases plasma levels of ropivacaine was measured but the toxic dose of ropivacaine could not be ascertained<sup>1-5</sup>. In our case we used ropivacaine at a dose of 2.30 mg/kg, which is below the standard toxic dose of ropivacaine (3 mg/kg), but still patient had central neurological complication (GTCS), showing individual variation in the threshold causing symptoms in healthy individuals<sup>1-8</sup>.

Though brachial plexus block with 0.5% or 0.75% ropivacaine with a volume of 40 ml was found to be safe, administering the minimal clinical effective dose reduces the risk of toxic effects<sup>5</sup>. In one study using nerve stimulator it was shown that 30 ml of local anaesthetic was effective in brachial plexus block<sup>9</sup>. The choice of local anesthetic was important and we chose ropivacaine because of its longer duration of action and better safety profile than bupivacaine. A summary of all case reports is given in table 1.

In this case, the serum drug concentration was not determined as the facility was not available in our hospital. However with no history of any illness like epilepsy or previous history of convulsions, with the presence of sensory and motor block which lasted for 240 minutes and the timing of seizures in relation to the administration of ropivacaine, the possibility of an intravascular injection, despite repeated negative aspiration of blood, could not be ruled out. Ultra sound guided nerve block is the method followed to visualize the structures before safe and effective administration of drug, so that accidental intravascular injection can be prevented.

## Conclusion

Though the adverse effects reported by ropivacaine are rare, precautions to be taken to prevent such events include—fractionating the total dose (two ml increments) of the drug and addition of epinephrine at a concentration of 1:2,00,000 (prepared and added separately) to local anesthetic solution thereby detecting accidental intravascular injection even if repeated negative aspiration was not confirmatory.

Recent advances like ultrasound guided nerve blocks with colour flow doppler, where we can visualize the structures more precisely can still reduce adverse reactions.

Repeated plasma concentration of ropivacaine can confirm the diagnosis, but its rarely done because of its limited availability.

## Summary

We report a case of generalized tonic clonic seizure without cardiovascular toxicity that was most probably due to ropivacaine used for brachial plexus block, which was effectively managed without any sequelae. It emphasizes that regional anesthetic techniques need to be applied very carefully and in appropriate settings with proper monitoring and all measures for early detection of intravascular placement of drug must be followed.

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# Case Report

## An Interesting Case of Hereditary Haemorrhagic Telangiectasia with Chronic Parenchymal Liver Disease

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### Abstract

Hereditary haemorrhagic telangiectasia(HHT) also known as Osler-Weber-Rendu disease is a rare autosomal dominant disorder that causes vascular dysplasias of all the blood vessels and results in a tendency for bleeding. It has a triad of mucocutaneous telangiectasiae, recurrent epistaxis, positive family history. We report a case of HHT in a 60 yr old male who was admitted with recurrent epistaxis, multiple mucosal and skin lesions, strong family history associated with chronic parenchymal liver disease which is a rare association.

**Key Words:** Hereditary Hemorrhagic Telangiectasia, Epistaxis.

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### Introduction

Hereditary haemorrhagic telangiectasia(HHT) is a rare genetic disorder having a prevalence of approximately 1 in 8000 people. It is manifested by vascular lesions like mucocutaneous telangiectasis and arteriovenous malformations (AVMs) which are a potential source of serious morbidity and mortality<sup>1</sup>. The diagnosis of HHT is made clinically on the basis of the Curaçao criteria<sup>2</sup>, which includes : a) Epistaxis b) Telangiectasias c) Visceral lesions d) Family history (a first-degree relative with HHT). Three out of the four criteria is diagnostic of HHT. Our present case met all the four criteria for HHT; recurrent epistaxis, telangiectasiae of the fingertips and tongue, GI bleeding from multiple vascular ectasias, and positive first-degree family history. Further our patient also had features of chronic parenchymal liver disease which is very rarely associated with HHT.

### Case Report

A 60 year old male presented with history of breathlessness of NYHA Class II, abdominal distention, bilateral leg swelling for 6 months. He had recurrent epistaxis since the age of 13, last episode being 1 week back. There was no history of haemoptysis, fever, abdominal pain, vomiting, or jaundice.

Patient had recurrent blood transfusions in the past for anaemia, was also treated for TB lymphadenitis in 1991 and for jaundice in 2003. Argon plasma coagulation was done for gastrointestinal vascular ectasias. Patient had undergone diagnostic laproscopy for an evaluation for ascites and treated for TB peritonitis in 2014. He is a known diabetic, non smoker and non alcoholic. There is family history of epistaxis and his grand mother died because of UGI bleed (Fig 1).

At the time of admission patient was severely anaemic with bilateral pitting pedal edema with a pulse rate 100/min and respiratory rate 24/min. Purpuric, punctuate tiny macules, blanching with pressure were noticed on fingertips (Fig 2), soft palate and tongue (Fig 3). Systemic examination revealed free fluid in the abdomen and hepatic bruit over liver. Cardiac auscultation revealed an ejection systolic murmur in pulmonary area.

His investigations revealed Hb-2.4 g/dL, ESR-150 mm/hr, Stool occult blood- Positive. HbsAg, anti-HCV, ANA were negative. UGI scopy and colonoscopy revealed gastric, duodenal, caecal and colonic angioectasias (Fig 4). USG abdomen was suggestive of chronic parenchymal liver disease with ascites. CT abdomen confirmed the features of chronic parenchymal liver disease in addition to the tortuous hepatic artery. Contrast echocardiogram with saline showed mild pulmonary hypertension without any pulmonary A-V malformation. Fundus- Roth spots in Lt eye probably due to severe anaemia. CT Brain was negative for A-V malformation.

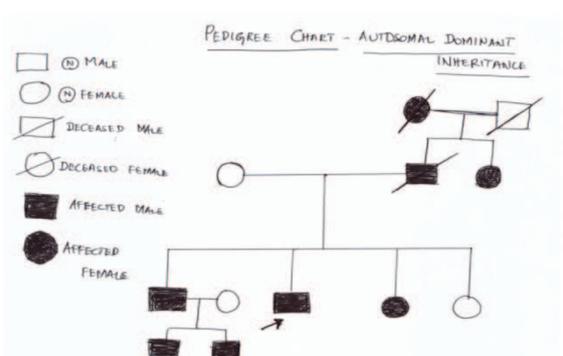


Fig. 1 - Pedigree Chart



**Fig. 2 - Telangiectasia on finger tips**



**Fig. 3 - Tongue Telangiectasias**



**Fig. 4 - Gastric Vascular Ectasia**

## Discussion

HHT was first recognized in the 19th century as a familial disorder with abnormal vascular structures causing bleeding from the nose and gastrointestinal tract. HHT is characterized by telangiectatic lesions in nose, lips, finger tips and visceral organs like liver, spleen, GI tract, genitourinary tract, lungs, brain, spinal cord. The most common clinical presentation is recurrent and severe epistaxis leading to severe anaemia which frequently requires transfusion<sup>3</sup>.

HHT is classified into four types genetically<sup>4</sup>. Out of the two major types of HHT (HHT<sub>1</sub> and HHT<sub>2</sub>) disease severity is more in HHT<sub>1</sub> than HHT<sub>2</sub>, with an earlier age of onset for epistaxis, mucocutaneous telangiectasias, and a higher incidence of pulmonary AVMs. HHT<sub>1</sub> can be induced by mutations in the gene, ENG (endoglin), encoding endoglin on chromosome 9q. HHT<sub>2</sub> can be induced by mutations in the gene, ALK-1 (activin receptor-like kinase 1), encoding activin receptor-like kinase 1 on chromosome 12q13<sup>5,6</sup>. They cause alteration in the elastic and muscle layers of vessel

walls, leads to spontaneous rupture and injuries<sup>7</sup>. Further, other minor types are associated with mutations in *madh4* gene (HHT with juvenile polyposis) and unidentified gene in chromosome 5 (HHT<sub>3</sub>). The clinical manifestations vary among families and sometimes may vary within the same family. Common clinical manifestations are shown in Table 1.

**Table 1 - Common Clinical Manifestations**

Epistaxis (90%) – most common
Skin and mucosal lesions (75%)
Pulmonary involvement (30%) – AV Malformations
Hepatic involvement (30%) - Jaundice, variceal bleed or atypical cirrhosis
GI bleeding (15%)
CNS involvement – Cerebral AVMs, Spinal AVMs

Management options are very limited. There is no definitive treatment for HHT as of now. Epistaxis could be treated with packing, aminocaproic acid, estrogen, argon beam ablation. Cutaneous lesions may be treated with electrocauterization with diathermy, hypertonic saline sclerotherapy, or laser therapy. Recently, limelight has been on Bivacizumab, a humanised monoclonal anti-VEGF antibody. It is given in the dose of 5 mg/kg as IV infusion for 4 weeks for reducing GI blood loss and epistaxis. Our patient was treated for chronic parenchymal liver disease with diuretics and symptomatically for epistaxis. To summarise, ours is a case of Hereditary Haemorrhagic Telangiectasia with a rare association of chronic parenchymal liver disease.

## Acknowledgement

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#### **For obese people, size does not matter**

To keep a check on how much we eat is not all that easy. One stratagem commonly employed by those who are keen to eat less, is to eat from a smaller plate, bowing to conventional knowledge that smaller plates carry smaller portions. But these acts of self-deception do not work for all. Particularly, it does not work for those who desperately need to eat less – obese teenagers. In a new study carried out at UConn Health Alcohol Research Center on teenage girls, the researchers discovered that the overweight subjects paid very little attention to the size of the plate or the container. Undistracted by the trick, they consumed until they felt full. They also failed to pay much attention to the detailed dietary charts. The only way to curb their appetite is to subject them to simple, clear, interesting and repetitive diet education. The study was presented at the Annual Meeting of American Psychosomatic Society.

[University of Connecticut. "Smaller plates, smaller portions? Not always." Science Daily. Science Daily, 27 March 2015]

- Dr. K. Ramesh Rao

# Case Report

## Advantage of Ultrasonogram in Perioperative Detection of Pneumothorax

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**Key Words:** Pneumothorax, Ultrasound, Perioperative  
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### Introduction

Pneumothorax is a potentially serious complication associated with blunt injury to the chest wall. Diagnosis is usually made with a combination of clinical signs and symptoms which may be subtle, and plain chest radiography. However supine chest x-ray has low sensitivity for traumatic pneumothorax. Diagnosis of pneumothorax in the perioperative area can be difficult due to lack of ready availability of equipments and trained personnel. Ultrasound allows anaesthetist to quickly rule out this potentially life threatening complication in the perioperative period<sup>1</sup>.

### Case Report

A 32 yr old man was brought to the casualty with history of trauma and blunt injury abdomen with tachycardia-102/minute, hypotension-90/60mmHg, tachypnea-28/minute and oxygen saturation (SPO<sub>2</sub>) of 96% with 4 litres oxygen along with diffuse tenderness, guarding and distension of the abdomen. Chest X ray showed multiple ribs fractures on left side with no evidence of hemo/ pneumothorax (Fig 1). With further deterioration of haemodynamic parameters, emergency laparotomy was planned.

On shifting the patient to the operation theatre, heart rate - 124 /min, non invasive blood pressure - 80/60 mmHg, respiratory rate - 30 /min and oxygen saturation was 85% with 100 % oxygen. With decreased chest wall movement, reduced air entry and a hyper resonant percussion note on left side, pneumothorax was suspected and an immediate bed side ultrasound was done. It confirmed the presence of pneumothorax with typical absence of lung sliding sign seen using brightness mode ( B- mode) and barcode sign using motion mode (M- mode).

On insertion of intercostal drainage tube( ICD), gush of air in under water seal was noticed, confirming the presence of pneumothorax. Oxygen saturation improved and air entry increased on left side immediately after ICD insertion. Surgery was commenced as planned under general anaesthesia. Haemoperitoneum of 2 litres with splenic injury was noticed for which splenectomy was done. With spontaneous and adequate respiratory effort along with stable haemodynamic parameters, patient trachea was extubated and shifted to post anaesthesia care unit with ICD tube in situ for postoperative monitoring. Postoperative chest x-ray shows ICD in situ (Fig 2).



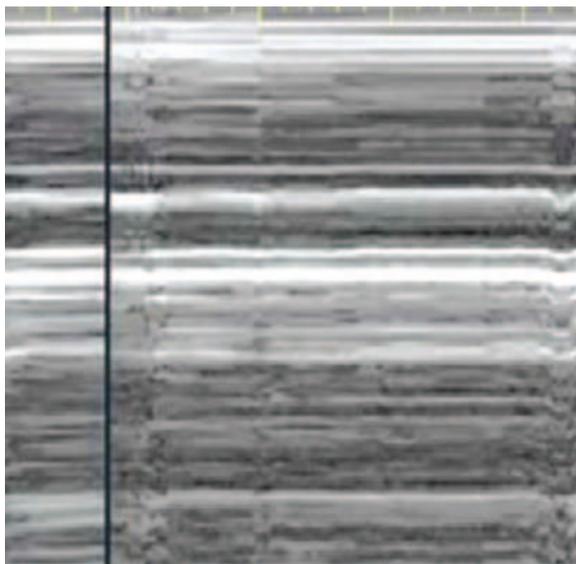
Fig 1 - Preoperative Chest X-Ray



Fig 2- X-Ray After ICD Insertion



**Fig 3 -** USG - Absence of comet tail sign



**Fig 4 -** Barcode Sign

## Discussion

Pneumothorax is the presence of air in the pleural space. It can be either spontaneous or traumatic. Traumatic pneumothorax may be due to penetrating and non-penetrating chest trauma. Diagnosis of a pneumothorax is based on clinical examination, chest radiography, and computed tomography (CT) scanning<sup>1</sup>. Pneumothorax is an uncommon and potentially dangerous problem, especially during general anaesthesia, when the patient cannot complain of respiratory difficulty or pain, and with positive pressure ventilation, which increases the risk of tension pneumothorax<sup>2</sup>. During the history and examination, the anaesthetist should be made aware of any precipitating factors that may put a patient at risk of a pneumothorax. Modalities for pneumothorax

detection are not readily available while patients are under general anaesthesia. The signs of a pneumothorax in a patient under anaesthesia can be nonspecific and difficult to interpret. Signs include difficulty in maintaining adequate ventilation, increased airway pressure, decreased oxygen saturation, hypotension, heart rate changes, distended neck veins, altered breath sounds on the side of the pneumothorax, and possibly unilateral chest expansion with tracheal deviation<sup>3</sup>. The application of positive pressure ventilation to even a small asymptomatic pneumothorax can cause progression to a life-threatening tension pneumothorax and addition of nitrous oxide can compound it<sup>1</sup>.

Computed tomography is considered to be the gold standard for detecting pneumothorax, but not possible intra-operatively because of few drawbacks like transporting patient to the scanner, need for a radiation technologist to perform the scan, time consuming, radiation exposure and cost factor<sup>4</sup>.

Traditionally, when a clinician suspects a pneumothorax, a chest radiograph is obtained. Chest radiographs are best at detecting a pneumothorax if obtained with the patient in the upright position, but this is not possible for the patient under anaesthesia. Moreover the radiographic appearance of a pneumothorax is dependent on gravity, anteroposterior supine radiographs may detect only a large pneumothorax<sup>5</sup>.

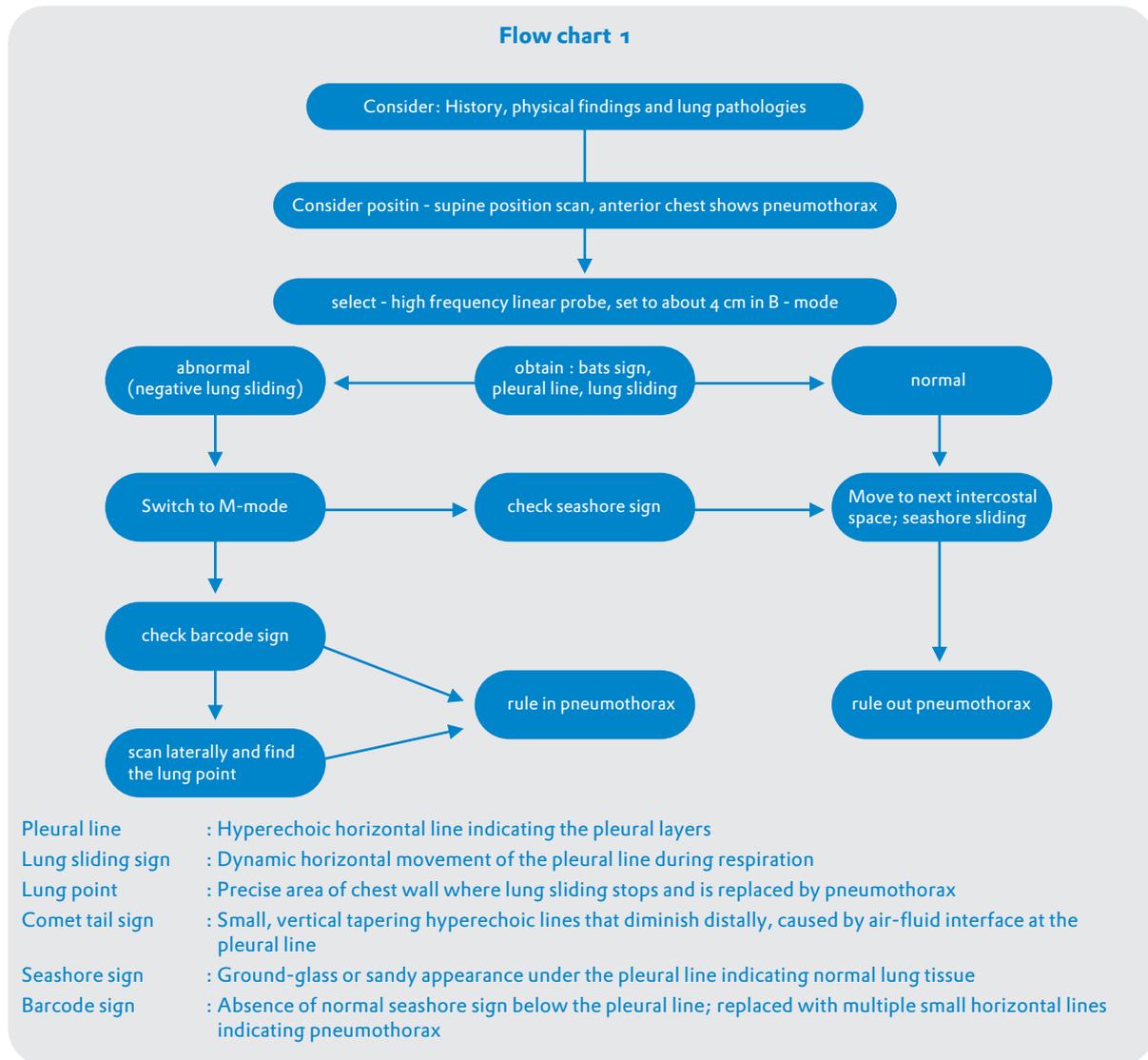
Portable ultrasonography has recently been studied for use in the detection of a pneumothorax. Sonography is a highly effective diagnostic tool that can lead to prompt intervention when life-threatening situations arise in the operating room<sup>6</sup>. Bedside ultrasonography is a sensitive screening test for detection of pneumothorax than supine chest radiography in the trauma patient. Ultrasonographic equipment is now easily portable and quickly produces high-quality images<sup>7</sup>.

The advantages are decrease in the time it takes to make a diagnosis, omission of radiation exposure to the staff and patient, reduction in cost, completion of diagnosis without the need for a radiologist and ease of use, but with some limitations like, chronic obstructive lung disease can mimic pneumothorax in ultrasound, Sensitivity and specificity can decrease after first 24 hour and in morbidly obese patient, the ultrasound resolution is poor.

## Modes In USG

Select a high-frequency linear probe and set the depth to allow viewing of the deep lung area. On most adults this should be at least 4 cm. Begin by selecting B-mode and place the probe on the anterior part of the chest. Obtain the bat sign showing 2 ribs in short axis and identify the pleural line. Check for lung sliding during any respiration (Lung sliding sign, Comet tail sign) (Fig 3). Each time an anomaly is seen, the image should be viewed in M-mode to check for the seashore or barcode sign (Fig 4)<sup>1</sup>. The various modes and its applications are explained in flow chart 1.

Flow chart 1



## Conclusion

The advantages of ultrasonography in diagnosing pneumothorax shows tremendous value to anaesthesia providers for use in the operating room and outweigh its few limitations. This case report describes a 32 year old male patient who was posted for emergency laparotomy for blunt injury abdomen, where ultrasound played a vital role in the operating room, diagnosing pneumothorax which was otherwise unidentified. This shows advantages and expanding role of ultrasonography for anaesthetists as an diagnostic, interventional, therapeutic tool in perioperative period.

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# Case Report

## An Interesting Case of Hemorrhagic Stroke with Absent Pulses

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### Abstract

Monckeberg's medial sclerosis is a degenerative disease of unknown etiology, characterised by dystrophic calcification of tunica media of small and medium sized arteries<sup>1</sup>. It is a poorly understood condition which can be associated with generalised atherosclerosis, coronary artery disease and chronic kidney disease. We report a case of Hemorrhagic stroke with absent peripheral pulses and extensive arterial calcifications. On extensive evaluation and ruling out various other causes, a diagnosis of Monckeberg's medial sclerosis as the cause was made.

**Key Words:** Monckeberg's Medial Sclerosis.

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### Introduction

Monckeberg's Sclerosis was first described by Johann George Monckeberg in 1903<sup>1,2</sup>. Because of calcification of tunica media, the blood vessel loses its elasticity and its capacity to dilate. The aetiology of this condition is not known. This condition is usually thought of as a benign condition. Here we report a case of Monckeberg's medial sclerosis presenting as hemorrhagic stroke.

### Case Presentation

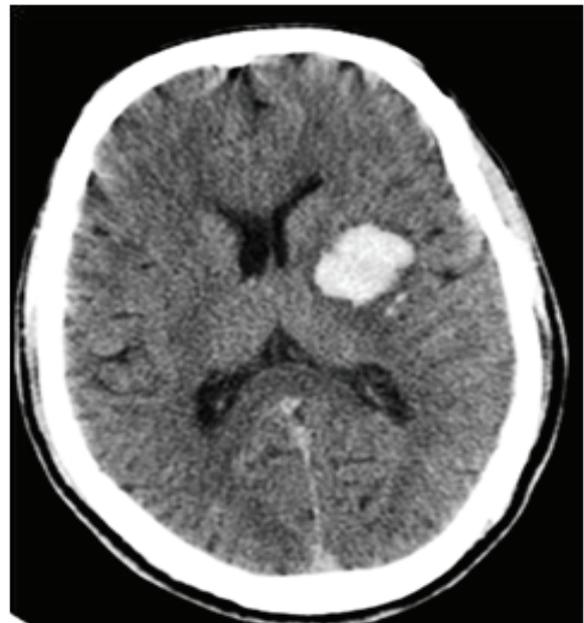
A 44 year old hypertensive male presented to us with acute stroke in the form of right sided hemiplegia. Except for high blood pressure there was no other contributory history.

On examination patient was conscious, oriented and afebrile. Pulse could not be felt in all four limbs while bilateral carotid pulses were very feeble. There was no evidence of limb ischemia. Blood pressure was not recordable by standard sphygmomanometer, and so it was measured by cardiac monitor which showed a blood pressure of 170/110mmhg. Neurological examination revealed a classical right sided hemiplegia with a spasticity of right upper and lower limb, with UMN type of right sided facial nerve palsy. Examination of other systems showed no abnormality.

### Investigations

Emergency CT –Brain was taken which revealed hemorrhage in left lentiform nucleus and internal capsule with mild surrounding edema (Fig 1).

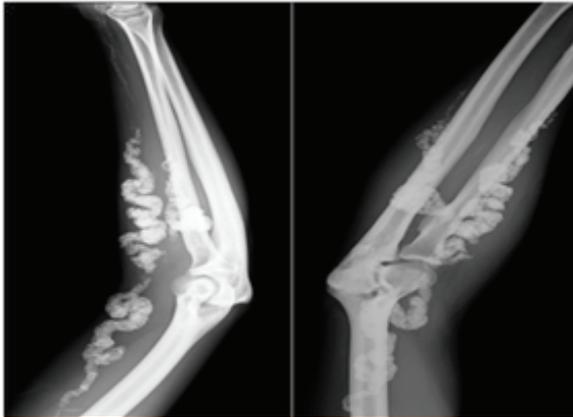
All routine biochemical investigations, ECG and chest X ray were within normal limits. To evaluate the absence of peripheral pulses Doppler Ultra Sonogram and X-ray of limbs were performed which revealed an extensive peri – arterial calcification (Fig 2).



**Fig 1 - CT – Brain revealing hemorrhage in left lentiform nucleus and internal capsule**

His echocardiogram showed normal LV function (EF – 60%) with no regional wall motion abnormalities, normal cardiac valves & chambers. His renal functions were normal. His Calcium – 9.1 mg/dl (N – 8.5 TO 11), S.Phosphorus – 4.4 mg/dl (N – 2.5 to 4.9) were normal. ANA by immunofluorescence was negative.

Magnetic resonance angiography revealed a contracted right kidney with poor visualisation of right renal artery. Mild arterial wall abnormalities were present in distal abdominal aorta along with poor visualisation of bilateral internal and external iliac bifurcations (Fig-3). Bilateral post tibial arteries were not visualized. Multiple cork screw collaterals were seen in both thighs.



**Fig 2** - X-ray limbs showing periarterial calcification



**Fig 3** - MR Angiogram - Poor visualisation of bilateral internal & external iliac arteries

## Treatment and follow-up

Since the patient did not have diabetes mellitus or chronic kidney disease or abnormal calcium and phosphate metabolism or suggestion for vasculitis, Monckeberg's medial sclerosis was considered as the reason for his arterial calcification. He was treated with antihypertensives and statins. Patient developed no further complications.

## Discussion

Monckeberg's medial sclerosis is a degenerative, non-inflammatory disease of unknown etiology which is characterised by dystrophic calcification of tunica media of medium and small sized muscular arteries<sup>1</sup>. Intimal layer of artery is spared and lumen is kept open by rigid calcified media, so there is no luminal narrowing<sup>3</sup>. Morphologically it typically affects arteries less prone for atherosclerosis. Arteries supplying lower extremities are more commonly affected<sup>4</sup>. Notably medial calcification has been reported to occur only rarely in coronary arteries<sup>5</sup>.

Usually it is an incidental finding in otherwise healthy elderly patients<sup>6</sup>. Plain x-ray radiograph may show pipe stem pattern and rail tracking<sup>7-9</sup>. Lumbar sympathectomy has been shown to promote occurrence of Monckeberg's sclerosis in lower limbs<sup>8</sup>. It's frequently associated with glucose intolerance, chronic kidney disease, old age, male gender and with autonomic neuropathy<sup>9</sup>.

It is postulated that such Monckeberg's medial calcification occurs due to loss of expression of certain proteins involved in inhibition of calcification like G1a protein, fibrillin 1, carbonic anhydrase etc triggered by a necrobiotic injury in vessel wall<sup>10</sup>. Other postulated mechanism being vascular smooth muscle cells having osteoblastic properties<sup>11</sup>.

Immunohistochemistry and in situ hybridization revealed osteoprotegerin immunoreactivity and mRNA expression surrounding calcified areas in the medial layer (Mönckeberg's sclerosis), whereas osteoprotegerin was mainly expressed adjacent to calcified neointimal lesions in atherosclerosis<sup>12</sup>.

Though coronary arteries are not commonly involved by this disease, there can be concomitant coronary atherosclerosis. Other investigations for diagnosis are ankle brachial pressure index and MR Angiogram or invasive carotid and peripheral vessel angiogram.

There is no treatment for Monckeberg's sclerosis. Trials with statins have failed to attenuate the rate of progressive vascular calcification. Trials with bisphosphonates are being tried<sup>12</sup>. Antihypertensives and statins are given to prevent progression of concomitant atheromatous plaque which may result in prevention of coronary artery disease and chronic kidney disease.

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### **Vitamin D likes fair skin!**

Worldwide, well over a billion people are deficient in vitamin D. As vitamin D directly influences muscle power, force of contraction and bone mass, it plays an important role in athletes' performance. However, until recently, no systematic study had been published regarding the prevalence of its deficiency in athletes. But now, researchers from University of Southern California have carried out a study in which vitamin D levels were measured in division I athletes. To their surprise, they found that nearly one third of those athletes had deficient levels of vitamin D (<32 ng/mL). The risk factors for the deficiency included male sex, Hispanic race, black race and dark skin tone. The deficiency appears to be 2.8 times more common in male athletes than in female athletes. However, after multivariate analysis, only dark skin remained as a significant predictor. The results of the study were presented at 2015 Annual Meeting of American Orthopaedics Association.

**- Dr. K. Ramesh Rao**

# Case Report

## A Rare Presentation of Chronic Myeloid Leukemia

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### Introduction

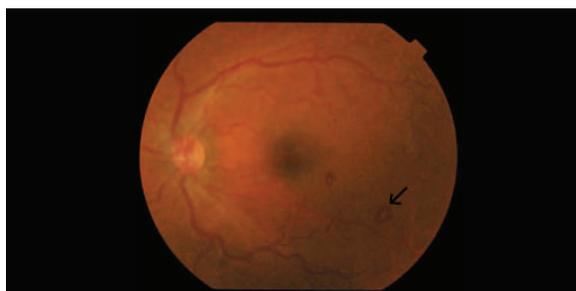
Chronic Myeloid Leukemia (CML) is a commonly encountered hematological malignancy, characterised by increase in erythroid, myeloid cells and platelets in the peripheral blood as well as marked myeloid hyperplasia in the bone marrow. The typical symptoms at presentation are fatigue, anorexia and weight loss, and the most common physical finding is splenomegaly. The presence of Philadelphia chromosome [t(9:22)] is the molecular abnormality found in 95% of patients. Imatinib, an inhibitor of BCR-ABL tyrosine kinase, is the standard treatment for chronic phase of CML<sup>1</sup>.

### Case Report

A 34 year old Indian male presented to ophthalmology department with bilateral progressive loss of vision of 5 days duration. Otherwise the patient was asymptomatic. No significant illness in the family. Fundus examination (Fig 1 & 2) showed bilateral white centred retinal haemorrhages (Roth spots). Hence patient was referred to medicine department for further evaluation. On physical examination he had pallor and massive splenomegaly. Examination of other systems was unremarkable.



**Fig 1** - Right fundus showing white centred haemorrhages



**Fig 2** - Left fundus showing white centred haemorrhages

His laboratory investigation revealed a haemoglobin of 8.8gm/dl with red cell count of  $2.6 \times 10^{12}/L$  and white cell count of  $2.85 \times 10^{11}/L$  (polymorphs 92%). His platelet count, ESR (12mm/hr) and urine examination were normal. The peripheral smear showed marked leukocytosis, basophilia and eosinophilia suggestive of chronic myeloid leukemia.

### Discussion

CML accounts for 15% of all leukemia<sup>1</sup>. It is a pluripotent stem cell disease characterized by anaemia, extreme blood granulocytosis and granulocytic immaturity, basophilia, often thrombocytosis and splenomegaly. CML usually presents with symptoms like easy fatigability, anorexia, abdominal discomfort, weight loss and excessive sweating. It rarely presents with isolated visual symptoms<sup>2</sup>.

Only 5-10% of patients in Chronic Myeloid Leukaemia present with eye involvement in the form of Roth spots, optic nerve oedema/pallor, retinal haemorrhage, retinal vein tortuosity, cotton wool spots and sea fan neovascularization<sup>3</sup>.

Other causes of Roth spots include subacute bacterial endocarditis, hypertension, diabetes, oral contraceptive use, systemic lupus erythematosus and multiple myeloma<sup>4</sup>. Subacute bacterial endocarditis is considered to be the commonest cause for Roth spots. However the presence of Roth spots should lead to search for other clinical condition such as leukaemia. We present this case for its rarity.

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# From the Pages of History

## Deliverance of One Genius by Another

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Dr. Subhash Mukherjee



Dr. T.C. Anand Kumar

On a fateful afternoon of 3rd Oct 1978, Durga, the world's second and India's first IVF baby was born in Calcutta, with the help of a team led by Dr. Subhash Mukherjee. This announcement was made 67 days after the birth of the world's first IVF baby, Louise Brown by Dr. Robert Edwards and Dr. Patrick Steptoe<sup>1</sup>. Dr. Subhash Mukherjee, the unsung hero of Indian ART, was born on 16th January 1931 in Hazaribag, Bihar. He was a medical undergraduate from Calcutta and Ph.D (Reproductive Physiology) from Calcutta University under the stewardship of Prof. Sachchidananda Banerjee. He had an ingenious mind and developed several techniques in ART which are still in use today.

### Some of his achievements are:

- Dr. Mukherjee along with Prof. Sumit Mukherjee, a cryobiologist, and Dr. Saroj Kanti Bhattacharya, a gynecologist, worked on a method of in vitro fertilization that was used successfully on a patient with damaged fallopian tubes. He presented his findings in the section on ovum implantation at the 5th International Congress on hormonal steroids held in New Delhi in Oct-Nov 1978<sup>2</sup>
- Developed an assay for estimation of Luteinizing Hormone (LH) which depends on ovarian cholesterol depletion of intact immature rats pretreated with PMSG & HCG<sup>3</sup>.
- Contradicted the view of Theodore Langhans on the origin of HCG<sup>4</sup>.
- He was the first to successfully use human menopausal gonadotrophins (hMG) for ovulation stimulation in an IVF programme. However, the credit for this was given to Dr. Howard Jones, USA, who discovered it three years later<sup>3</sup>.
- Dr. Mukherjee was the first to approach the ovaries via the vaginal route by posterior colpotomy<sup>3</sup>. He was the first person to have succeeded in freezing and thawing human embryos using a cryoprotectant (DMSO) which is now very commonly used for freezing embryos<sup>2</sup>. Sadly, even this credit went to the Australian team headed by Dr. Trounson for making this discovery in the 1980s<sup>3</sup>.
- Dr. Mukherjee was the first to have aspirated oocytes in a stimulated cycle, fertilize them in vitro and freeze the embryos in that cycle, recover and thaw and transfer them into the uterus during the following natural cycle, which led to the birth of Durga<sup>3</sup>.

Despite such phenomenal achievements of Dr. Subhash Mukherji, he did not receive the credit he was due; on the contrary when he addressed his findings by letter to the West Bengal Government in 1977, his claim was denounced as bogus and was ostracized by the government. Adding insult to injury, he was transferred to the Regional Institute of Ophthalmology, Kolkata, in June 1981 after which he committed suicide<sup>6</sup>. It is a tragic moment in the history of Indian science when the efforts of a genius were not only unrecognized, but denounced.

Fortunately, his phenomenal work could see the light of the day due to the nobility of Dr. T.C. Anand Kumar, who led the team which gave India's first scientifically documented IVF baby<sup>7</sup>.

Dr. T.C. Anand Kumar, a graduate from Bangalore, did his doctorate from the University of Jodhpur and then went on to Birmingham, UK to pursue his research. He was known not only for his scientific achievements but also for his warm personality<sup>8</sup>.

When he was invited to deliver the Subhash Mukherjee Memorial Oration at the third National Congress on ART and Advances in Infertility Management in Calcutta on 8th Feb 1997, he researched about the birth of first test tube baby. He had known earlier about the IVF baby from Kolkata through a report in Nature by K.S. Jayaraman. He also learned that this achievement was denounced as bogus. Dr. T.C. Anand Kumar investigated by further procuring some of Dr. Mukherjee's handwritten laboratory notes, list of publications and papers presented at various scientific meetings and his various correspondences and notes left behind by him<sup>9</sup>. Having gone through all of it, he convinced the ICMR committee to acknowledge Durga as the country's first IVF baby.

The ICMR committee after thorough investigation now firmly believes due credit was not given to Dr. Subhash Mukherjee for his work. Dr. P M Bhargava, former Director of Centre for Cellular and Molecular Biology, who was part of the ICMR investigations, has called Dr. Subhash Mukherjee as the Father of Indian IVF.

Apart from bringing to light a major scientific achievement, Dr. Anand Kumar contributed significantly to ART.

### Few of his achievements and awards are<sup>8</sup> :

- He started the first electron microscopy laboratory and the neuroendocrine research laboratory at the All India Institute Medical Sciences, New Delhi, in 1970 which is still functional today.
- Founded the Indian Society for the Study of Reproduction and Fertility in 1988.
- He served as an advisor on many committees on the World Health Organization, Department of Science and Technology, Council of Scientific & Industrial Research, Government of India; Department of Biotechnology, Government of India and, of course, the Indian Council of Medical Research till September 2009.

- Contributed in drug delivery through nasal route.
- Instrumental in formulating the ICMR's National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India.
- His work was recognized by his peers and he received the Shanti Swaroop Bhatnagar Award, the highest scientific award for mid-career scientists in the country and the Sanjay Gandhi National Award.

Dr. Anand Kumar later retired to Bangalore where he opened HOPE infertility clinic, through which he has made immense contributions. Though he passed away in January 2010, his scientific contributions stay alive in all our memories.

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### Sugar sensing MRI detects sugarless cancer

One of the co-inventors of NMR, Raymond Damadian devised MR scanning machine in 1977 to detect early cancer. Although the MRI, a derivative of that machine, has been extensively used in oncology, detection of early cancer is not one of its forte. But that may change in near future. In a new study published by the John Hopkins researchers in *Nature Communications*, mucins with or without attached sugar were compared between normal and neoplastic cells using an MRI configured to detect sugar. They found that the mucin-attached-sugars were markedly lower in cancer cells compared to their normal counterparts. It seems that the cells when they become cancerous, lose the sugar attached to some of the surface proteins. If their results are confirmed, MRI may indeed become an important tool in the early detection of cancer and also to monitor response to cancer chemotherapy.

(Label-free in vivo molecular imaging of underglycosylated mucin-1 expression in tumour cells, Xiaolei Song, et al., *Nat. Commun.*, doi: 10.1038/ncomms7719, published online 27 March 2015).

- Dr. K. Ramesh Rao

# Dialogue with the Stalwart

## Interview with Dr.B.N.Chakravarty

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Dr.B.N.Chakravarty

**We have heard about your great love for teaching, Sir. So what has been your inspiration to join this field?**

Initially, I didn't have much interest to join this IVF discipline, I was working as a clinician, as a gynaecologist and obstetrician, doing surgeries partly related to infertility. I was doing a lot of oncology surgery. In 1970's, there was no radiotherapy, or chemotherapy, so I had to do oncology radical, ultraradical surgeries. But that did not give me an incentive as the results were not very good. While doing that I learned the technique of fine dissection of the tissues, so I moved on to congenital malformation of the female genital tract, because that was also an area that was not touched upon by the ordinary gynaecologists.

I saw a case; a small girl coming with primary amenorrhoea, of 15-16yrs, the defect was absence of vagina, absence of uterus; at a stretch I had to construct the uterus because of absence of mullerian knobs. For all these young girls of 13-15yrs there was no treatment available. So I took up those cases and started doing re-constitutive surgery, very few reports were there all over the world. I could do re-constitutive surgery of the vagina which went quite alright, and united the two mullerian knobs inside the pelvis with the hope that they will menstruate and finally have a pregnancy. In 1967-68, I presented that paper in Switzerland. It worked well as far as menstruation was concerned, but they didn't have a pregnancy. There is another type of malformation simultaneously seen in these patients, that they had an uterus but not the lower part of the genital tract i.e, the cervix was absent, the vagina was absent.

So I could at least restore the sexual function by creating a vagina, but the menstrual function was absent. They had a functioning uterus and they had the menstrual function as well but invariably, in majority of these girls, cervix used to be re-stenosed, re-operated, so for some or the other reason it went on for some time but finally around 2 girls conceived. I did around 25-30 surgeries on such cases. Until the age of 70 or 75, I went on doing these surgeries and almost all of them had menstrual cycle re-established but 3 of them got pregnancy. That was reported in American Journal of Gynaecology in 2000.

During that period I came in contact with Dr.Subhash Mukherjee. I was presenting and publishing all these papers in scientific conferences when he heard about me. He created an interest in fertility in me and that is how I joined this field. While I was trying for a pregnancy after a surgical correction, he was trying for pregnancy after medical treatment. He was a physiologist, not a gynaecologist. We were both in Govt. Medical service. In one institute, the NRS medical college we were posted together, he was the Asst. Professor of Physiology and I was the Asst. Prof. in Obstetrics & Gynaecology. So we used to hold meetings very frequently, and gather all these cases; from my side all the congenital abnormalities and on his side, Turners syndrome, testicular feminizing syndrome, PCOS, and congenital adrenogenital hyperplasia. Every week we used to run a clinic and about 30-35 patients used to come there. We used to do investigations, give medical treatment and gradually that made me interested. I had no idea about endocrinology because I was a very blunt cutter, but he created interest in me.

Anyway, at that time in 1974-75, Dr.Mukherji was reading journals with publications of Dr.Stepto and Dr.Edwards and he used to talk about test tube baby of which I had no idea at that time. We went to Tokyo, Japan together, for a world conference where I presented my paper on hysteroplasty, vaginoplasty and he presented his paper on stress induced PCOS. Anyway, both of our papers were appreciated in that conference and it appeared in journals and papers also, it came out very well in the conference bulletin saying that, from India, two papers have come and were applauded very much. Later he published a paper reporting the birth of a test tube baby, Durga, on Oct 1978, 3 months after the test tube baby in England, Louise Brown, that of Robert Edwards and Stepto. Till 1978, he was criticized all over the country, all of us know that tragic story. He got very depressed because of all things coming up, and finally committed suicide. After that his wife came to me asking to carry on his work and that people should not call him a liar. I promised to continue his work and that was how I entered into the field of IVF, not intentionally but circumstantially.

When I was invited to deliver lectures outside, in India and abroad, people did not believe my work and started doubting me which was very upsetting. But that gave me strength, I took it up as a challenge and wanted to prove that it can be done in India. So I formed a team with young doctors and started the work together. At that time, nothing was available in India, not even the embryo transfer catheter, not to speak of the culture media. We did not know about the media, nor about the CO<sub>2</sub> cylinder.

### Your team had developed a new technique for a CO<sub>2</sub> incubator back then.

Yes, we used to pump in our exhaled air to the embryo culture as exhaled air contains CO<sub>2</sub>, and the oxygen from the oxygen cylinder. There was a baby incubator, but that did not bring us success as the embryos used to become dark. The media was not available; we started with Tyrode's media and Hams F12 was available in Mumbai, for which we used to travel to Mumbai to get, and even the MilliQ water was not available. We used to prepare the media ourselves. So, from Bangalore, we got the Millipore filter and started filtering. That was our beginning. We started reading endocrinology voraciously. I still remember the book, Ganong's; it was very basic and interesting book. But for the equipment and consumables we faced a lot of trouble as we could not import anything during those days without an import license. For plastic materials alone at that time, we used pay tax of 300%.

In 1982-83, the first international conference was held in Helsinki, Finland, where I presented a paper along with my embryologist. My paper was accepted there. We presented the first cleavage embryo that resulted in a biochemical pregnancy. The first baby was born in 1986, Imran, the first viable baby.

### Ever since you have achieved a lot over the years.

Yes, I devoted myself to IVF, I gradually gave up even Gynaecology. We formed a very good team and they supported me like anything. After we got the first test tube baby the government supported us by allotting an area, a very calm place, it was more or less a car garage, in which we turned into laboratory, In 1992 we got some freedom; we got the import license when Manmohan Singh was the finance minister. Until then it was hush-hush type of experience, and the patients also were very scared. They used to hide that it was a test tube baby. In the society that was not accepted back then.

### Even India's first IVF baby, Durga, was also kept secret for a long time.

There was always a belief that for a test tube baby, semen always came from a donor. I don't know wherefrom that false, erroneous concept came. That was one of the major difficulties we faced.

### How did your interest come about in antioxidants for male infertility, to increase sperm production?

We got a luminometer and measured the pro-oxidants, and oxidative stress on asthenozoospermic subjects, we could count the limit of stress. And we used to add vit.E, vit.C, and Apo co-enzyme and see remarkable improvement in vitro. We have done a study which we will be publishing in next ISAR. We were using both nutraceuticals and antioxidants but while using in vivo, no improvement was achieved.

### What do you think about multiple drugs, like lycopene, arginine, carnitine, used for male infertility?

They are still empirical. Each of the antioxidant has different functions, some provide nutrition, some provide metabolic functions, some provide metabolic respiratory function, and some of them provide locomotion. These functions must be there, following which, the sperm can fertilize. The sperm has a long way to travel, from the seminiferous tubules to the fallopian tubes; there are so many turbulences on the way, but the function should remain intact during these turbulences. Unless the DNA is compact it cannot withstand all the turbulences on the way. And it must remain active. For this activity you require antioxidants.

### ICSI used to be done for severe male infertility, but nowadays ICSI is done for all patients, do you feel IVF has started deteriorating, going the GIFT way?

Not everybody believes in that particular dictum – 'All ICSI, no IVF'. Though we have no particular evidence, ICSI may do some damage. Afterall, it is an invasive procedure, and a non-selective procedure. Always there's a sperm selection, and there are 4 stages of sperm selection – vagina, uterine tract, cumulus corona mass and zona pellucida. The best sperm, most vital sperm must fertilize the oocyte.

And that is surpassed in case of ICSI. ICSI does not believe in that. They are of course trying to isolate the best looking sperm, but only morphologically, no biochemical tests are done. In all the sperm function tests, nothing is biochemical, excepting HOST. Nowadays we have IMSI, PICSI, but still not the best sperm can be selected. But you are getting pregnancies, and babies also do not have any congenital defects; so though there are so many arguments against ICSI, you cannot prove that ICSI is bad.

### But all the first ICSI babies are reaching the reproductive age only now. So only now will we get to know if they are normal. What about your IVF baby, Imran, he must be around 27 now, is there still a follow up?

Yes, I heard he got married and he's got a child now. But he's not keeping in touch with us, for the same reason. Those days, the prejudice was there, he was from a village and his mother was afraid that the people will think he's not her boy, or they wouldn't have used her husband's sperm. And our next baby in 1989, Suraj, was from Kerala, he's also very good, as far as intelligence is concerned, but he's still in college.

### Which do you feel is better, Day 3 embryo or Day 5 embryo? Your view.

It all depends; day 3 and day 5, both are good. Two points must be highlighted, one being the quality of the embryology lab, that must be very good and the second one is the patient and cycle characteristics. The cycle characteristics are that in that particular cycle, how many eggs were retrieved and on day 3 how many eggs have gone upto 10cell stage? So if more than 2 have gone, then I think day 5 can be done. Less than three is better to do day 3.

### Nowadays, people have started to follow 'freeze all' technique for embryos, your opinion.

The dictum is coming, but I am not very sure. The same thing follows, the quality of the lab, you must be very confident of the culture lab and also about your vitrification procedure, and the recovery rate. And our recovery rates are not as good as what have been suggested by the papers. In my lab, I would not allow that unless I am very confident.

### Suppose you were very confident, then would you go ahead.

Yes, theoretically, it holds good. In a stimulated cycle, the quality of the endometrium is not that good as the natural cycle, so that holds good. But there are some objections, opposing that, even in presence of high levels of progesterone and estradiol, the pregnancy rate is not bad. But the consensus is, in a stimulated cycle the endometrium is antedated and not coinciding with the blastocyst formation.

### In cases of unreceptive endometrium, do you think assays like Endometrial receptor assay(ERA) will be useful?

No, I don't think it is of any practical use; theoretically, yes. Since the endometrial bit is taken in the pre-conception cycle and not the treatment cycle, it does not hold good. And you cannot take in the treatment cycle as it might disturb the endometrium. But there is an opinion for that, traumatizing the endometrium in the pre-conception cycle will bring out better receptivity. But I have no confidence in that. To touch the endometrium during the conception cycle is very risky, and the endometrium varies cycle to cycle, and genes expressing will vary, the steroid level also varies, and it would depend on the nature of stimulation given. They are all vague areas, which have to be explored by non-invasive methods.

We are trying to get non-invasive markers, we are currently working on uterine fluid, maternal serum and follicular fluid. Follicular fluid will be the best marker because I believe that good oocyte will produce a good embryo and a good embryo through dialogue with the endometrium will give better receptivity. A good oocyte will develop in good environment and good environment is good follicular fluid, so the markers of the follicular fluid can predict if it is a good oocyte or bad oocyte. Similarly, AMH, estradiol, IGF-1, plasminogen are good markers, MMP, all these markers, we are trying to correlate them, with pregnancy. The follicular fluid is a gold mine.

### The drugs used for stimulation, would you prefer urinary or recombinant?

That is more or less clarified, excepting preconditions like over down regulatory cycle, or long protocol down regulation, in that case any drug you can use, over down regulatory cycle you have to use HMG, and LH and second one is poor ovarian response, you also require some LH, and in elderly ladies with less amount of testosterone which means less amount of LH, these are the 3 groups of patients who require a definite initial stimulation with urinary HMG, rather than recombinant FSH/LH. In normal responders, you have a choice, FSH is better, I think.

### As for your achievement of conception in a 50 yr old lady which was reported in the news recently?

That is another area which we are working, recurrent implantation success as against recurrent implantation failure, which is a common thing. Not only this lady, before this we had another lady who had 10 times implantation, she was getting pregnant every time, but the pregnancy was not going to term. This 50yr old lady also, she had two attempts, the first attempt also was an implantation success, but it ended in a miscarriage at 8-10wks. The second time also she got pregnant. So she was a woman with a favorable embryo and favorable endometrium, clicking together. So we are thinking that there must be a difference between the couples, in the whole society. Some couples conceive within the first month of marriage, some couples take six months, why is this difference? They do not use any contraceptives or fertility improving drug, and yet do not get pregnant. This fertility index also exists in infertile patients. We are trying to get genomic or metabolomic differences between these couples of recurrent implantation success and recurrent implantation failure.

### In today's practice, everyone is doing sperm DNA integrity test and they are giving medications accordingly, what is your view? Is it worthwhile conducting the test?

I have no idea. Practically it is not possible. Excepting for IMSI, All the other tests are biochemical in which we'll be losing the sperm.

### ART guidelines then and now.

I am not very happy. Back then we started the guidelines so that people will follow it strictly, but it is not being followed at all. Especially, they are playing with the third party reproduction, the oocyte donor and surrogacy. It has become a business.

### What does the future hold for ART?

It will be very good. Barring some areas, it is opening up so many things, particularly in the field of male infertility, endometriosis, endometrial receptivity. You know the problem but you don't have the solution, so proteomics and genomics will help us.

### What would be the advise you would give for all your students?

Teaching is a habit, and by teaching you learn, you rectify your mistakes. No teacher has 100% knowledge. In one word, self audit- don't think you know everything. You learn by teaching; when you stand on a dais and talk there are some areas you would not be able to explain. This makes you think if there is some deficiency in your knowledge or deficiency in your expression. No one can teach you that. You have to learn it yourself.

## News and Views: The Promise of Vaccinology

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### Introduction

In the early days of vaccination, the field weathered the share of criticism due to any scientific advance. The positive outcomes of vaccination were balanced by the ambiguity of statistical evidence for its safety<sup>1</sup>. Alfred Wallace who co-discovered Evolution with Darwin, advocated the exercise of caution<sup>2</sup>. Anti-vaccinationism found a place in the Nazi theories of racial superiority and exploitation of evolutionary theory. Sample an argument: 'Immunity to disease indicates that the individual is robust, therefore vaccination prevents the operation of natural selection. 'Such objections are perverse and at odds with the chief object of medicine, namely to provide succour to the sick<sup>3</sup>. The utility of vaccination as a method to create memory in the immune system using the agent of disease itself but without its virulence factors is today firmly established. Vaccine research has yielded effective prophylaxis in many cases. We are heavily anticipating vaccine breakthroughs for many more conditions, including some cancers.

### Hurdles to effective vaccination

- Design of the vaccine: A balance must be achieved in the attenuation of the virus/pathogen to be used as the agent of vaccine. Too attenuated, and the memory might become non-specific and not of much use. Too virulent, and the vaccination might itself lead to complications. The polio vaccine, a genuine triumph of vaccinology, was falsely associated with risk of seizures and neurological conditions. More recently, claims that autism and developmental regression were associated with the long-term sequelae of childhood measles-mumps-rubella vaccination have been thoroughly debunked<sup>4</sup>.
- Coverage of vaccination: If a sufficiently large fraction of the population is vaccinated, then the un-vaccinated proportion of the population could be protected against the disease through a phenomenon known as herd immunity. If more members of the population remain unvaccinated, then herd immunity breaks down. A fine line separates the emergence of herd immunity and the outbreak of disease.

### Optimising vaccination

To draw a simple analogy, consider insurance. Ideally everyone (i.e. 100%) should be covered, but in practice there will be the uninsured few among us. In the context of vaccination, suppose we have an effective vaccine against a certain infectious agent. If more parents in the population are phobic to vaccination, then the personal decision to vaccinate is biased, and one could skip vaccination, instead relying on herd protection. This will lead to the incidence of the disease in the population, and an outbreak of the disease in the worst case.

An alternative scenario consists in viewing vaccination as a public good where the state mandates a policy of compulsory vaccination. This interpretation involves the following caveats:

- Citizens should be wary of fallacious policies imposed by compulsory legislation;
- On the other hand, public goods are not adversarial to personal freedom. For example, consider a state policy of net neutrality – where the internet remains open for everyone's access and free from corporate manoeuvrings. This is essential to a democratic internet.

If vaccination is enforced by the government as a public good, it could eventually lead to the elimination of the disease reservoir. This strategy is not free of controversy. Even if the disease were controlled below its basic reproductive ratio<sup>5</sup>, a latent reservoir of the pathogen in just a very few individuals could form the testbed of evolution. In the absence of absolute coverage, the selection pressure for the emergence of resistant pathogen strains is active and forceful. In the event that resistance emerges, the virulence of the pathogen might likely be amplified, leading to a serious question of public health, and a challenge for biomedical research. The evolution of resistance poses one of the key challenges for medicine in this century.

### Conclusion

Strategies for vaccination must be optimized to control the outbreak of crises in public health. For life-threatening infectious diseases, complete coverage of vaccination is our surest ally. Planned mass immunization could help avert the recurrence of disease in the population. In complementation with the safety of vaccination, the treatment of disease at its source would be the appropriate requisite.

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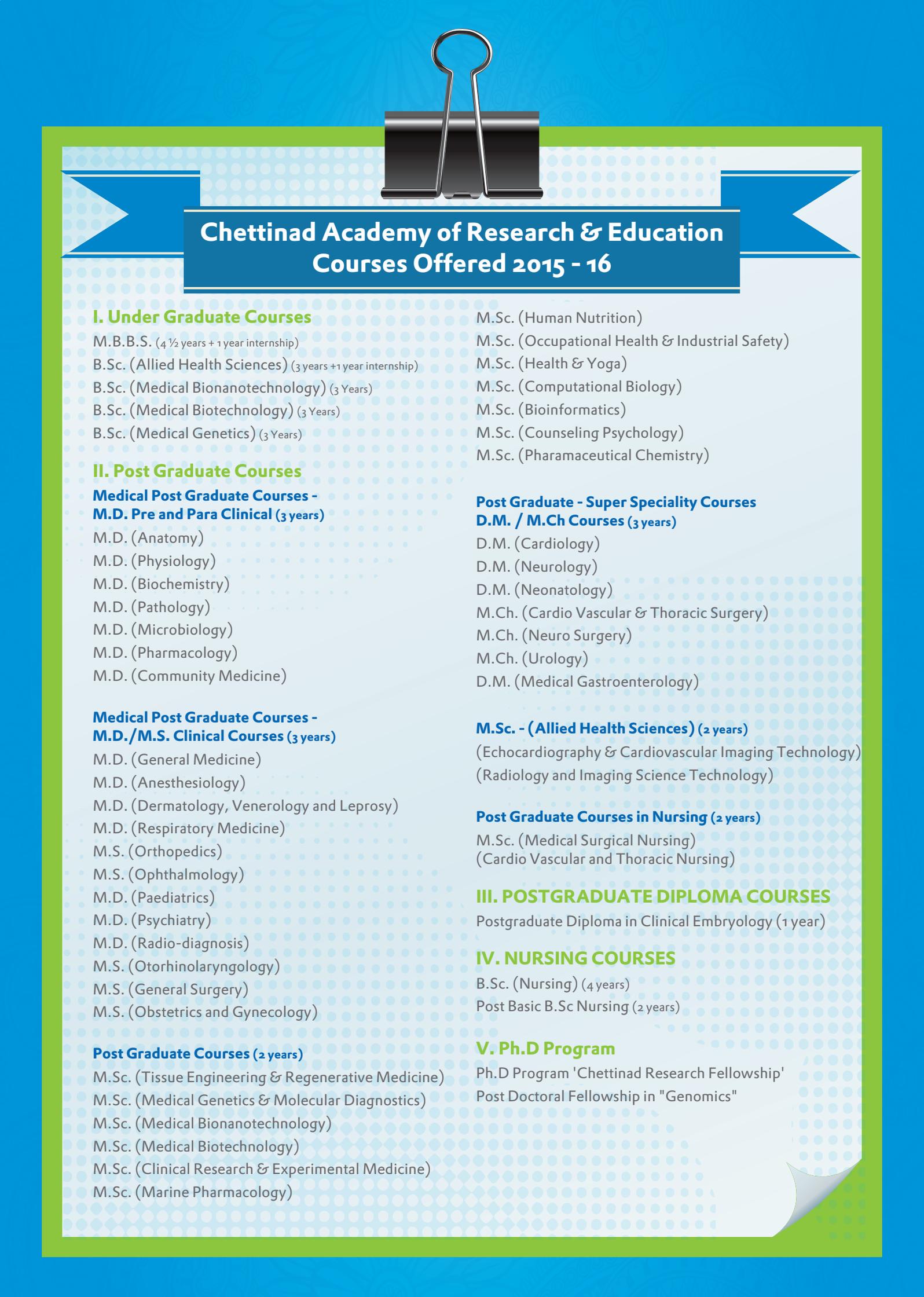
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