pISSN NO. 2277 - 8845
eISSN NO. 2278 - 2044

Chettinad Health City

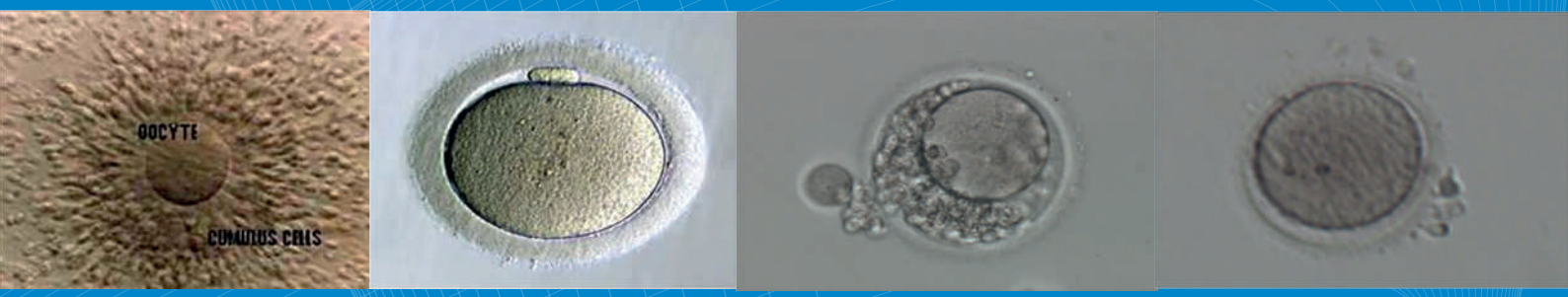
Volume - 1, Number - 1,
January - March 2012

Chettinad Health City

MEDICAL JOURNAL

www.chettinaduniversity.com/journal

In this issue



All rights are reserved

Chettinad Health City Medical Journal is published by Chettinad Academy of Research and Education.

Apart from the fair dealing for the purposes of research or private study, or criticism or review, no part of the publications can be reproduced, stored, or transmitted in any form or by any means without the prior permission.

Chettinad Health City Medical Journal and /or its publisher cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal. The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and / or its publisher of the quality or the value of the said product or of claims made for it by its manufacturer.

EDITORIAL OFFICE

Dr. N. Pandiyan
Chief Consultant, IVF
Chettinad Health City
Rajiv Gandhi Salai, (OMR, Chennai),
Kelambakkam, Kanchipuram Dist
Tamil Nadu - 603 103
India
T. +91 (0)44 4742 8300
F. +91 (0)44 4741 3343

Email:
chettinadhealthcityjournal@gmail.com

PUBLISHED BY

Chettinad Academy of Research and Education

WEBSITE

www.chettinaduniversity.com/journal

All disputes within the jurisdiction of the Madras High Court only

Chettinad Academy of Research and Education (CARE)

Dr. M.A.M.Ramaswamy
Chancellor - CARE

Shri M.A.M.R. Muthiah
Trustee - CARE

Dr. V. Raji
Vice Chancellor - CARE

Mr. SPK. Chidambaram
Registrar - CARE

Chief Editor

Dr. N. Pandiyan

Associate Editors

Dr. K. Ramesh Rao
Dr. Pradeep G. Nayar

Assistant Editors

Dr. Anitha.V
Dr. Thilaka Muthiah

Editorial Advisors

Dr. K. Ravindran
Dr. R.M. Pitchappan
Dr. P. Rajesh
Dr. L. Lakshmi

Section Editors

Dr. Ashok Palaniappan
Dr. Balaji T.K
Dr.Ganesan.R
Dr. Jeya.M
Dr. Jothi Ramalingam.S.B
Dr. Lailu Mathews
Dr. Mahendran V.S
Dr. Malligai.E
Dr. Manohar.C
Dr. Murali.R
Dr. Murugesan R
Dr.Narayana Reddy.M
Dr. Natarajan.A.S
Dr. Pandurangan R
Dr. Rajasekaran D
Dr. Ramnath Shyamala
Dr. Ravi Kumar R
Dr. Ruckmani.A
Dr. Srinivasan .B
Dr. Srinivasan M S
Dr.Thayumanavan S
Dr. Vasantha N Subbiah

IT Support & Design

Mr. S.M. Michael
Mr. Ramesh Palaniappan
Mr. S.T.Manigandan (Designs)

Legal Support

Mr. Balaji

pISSN NO. 2277 - 8845
eISSN NO. 2278 - 2044

Chettinad Health City
MEDICAL JOURNAL

Contents

Editorial

Vanakkam, Namaste, Greetings.

Welcome to the first edition of Chettinad Health City Medical Journal. You may wonder why we need another Medical Journal when we have a plethora of Medical Journals.

The Core Committee also dwelt on this point and felt there is indeed scope for another Medical Journal particularly to address the explosion of Medical Knowledge and Medical Technology in different fields of medicine.

Chettinad Health City Medical Journal will be a peer reviewed journal. The journal will have different sections addressing the medical students in their final years, the General practitioners & Specialists early in the career.

The journal will have the following sections:

1. Original articles
2. Review articles
3. Case study
4. Perspective / Opinion articles
5. Interview with eminent Medical/ Health Personality
6. Interesting ECG
7. Class rooms/ Student Tutorial – A topic of interest to the Undergraduate students
8. From the pages of history
9. Medical/Laboratory instrumentation
10. Medical Hypotheses
11. Debate

The first issue of the journal is addressing "Oral Health". Oral Health can be a reflection of our body's health. Poor oral hygiene has been implicated in many conditions like pre term labour, coronary heart disease, osteomyelitis, dermatological conditions, to name a few. Therefore it is essential to maintain oral health for the overall health of the human being.

An original article outlines the different oocyte abnormalities encountered in an assisted reproductive technology programme.

The current issue carries two review articles. The first review article on " Inflammation in acute coronary syndrome" outlines the role played by inflammation. Inflammation is an integral part of many pathological processes. It is probably the final common pathway in many conditions. The article describes several different pathways involved in inflammation in acute coronary syndrome.

The second article reviews the relation between osteoporosis and periodontitis. Osteoporosis is a "pandemic". Reduced exposure to sun, changes in life style and food habits may all contribute to osteoporosis. The article indicates that periodontitis and mandibular bone loss may be early indicators of osteoporosis.

There are several interesting case reports. There is a case report on " Seckel syndrome". The case report on "Gastric volvulus" with wandering spleen, emphasises the life threatening nature of the condition. Missing anterior teeth is often a social stigma. A case report outlines the management of missing front teeth.

The class room article on "Acute abdomen" describes the management of the condition as we see in our clinics.

Medical update highlights several current publications from around the world, which are of immediate concern to all of us.

The tale of two symbols from the pages of history clears the confusion around the medical emblem.

I hope you will enjoy going through the issue. Please do give us your valuable feedback.

Dr.N.Pandiyan

Editor : Chettinad Health City Medical Journal

E-mail : pandiyan1@yahoo.com

Perspective Article

Semen Analysis - A Numbers Game

Dr. N. Pandiyan, Chief Counsultant, Dept. of Reproductive Medicine, Chettinad Super Speciality Hospital

Chettinad Health City Medical Journal 2012; 1(1): 2 - 3

Semen Analysis, despite its limitations, remains the single most important test for evaluating male fertility. However, the test is prone for errors at all levels of its performance.

There could be collection artifact, performance artifact or reporting artifact. Semen collection which looks like an apparently simple act, is fraught with many difficulties for infertile men and impossible for other infertile men. Since the discovery of the spermatazoa by the Dutch microscopist, Antonie van Leeuwenhoek in 1677A.D[1] several methods have evolved to estimate a semen sample[2,3]. Several parameters have been described in a semen sample. However all these parameters have not yet been standardized and the values differ in different populations.

The WHO has published five editions of the manual for semen analysis at different times. The standards & reference value for different parameters have been redefined with each subsequent new edition. The first four editions were based on 'Consensus from experts.' and not on evidence based data. While consensus is suitable for social situations, consensus is bad for science. The current edition[4] – Fifth Edition has redefined many of the values based on multicentric study; however, the manual does not take into account the ethnic differences (e.g. not involving Indians), many men previously considered to be Oligo, Astheno, Terato Zoospermia are now considered to be normal. Table 1.

Parameter	WHO 1987 (2nd edition)	WHO 1992 (3rd edition)	WHO 1999 (4th edition)	WHO 2010 (5th edition)
Volume	2.0 ml & above	2.0 ml & above	2.0 ml & above	1.5 ml & above
Sperm Concentration (million/ml)	20 million & above	20 million & above	20 million & above	15 million & above
Total sperm number (million/ejaculate)	40 million & above	40 million & above	40 million & above	39 million & above
Motility	50%(A+B) & above, 25% or more with Rapid progressive	50%(A+B) & above, 25% or more with Rapid progressive	50%(A+B) & above, 25% or more with Rapid progressive	40% (PR-32%)
Morphology	50 % & above	30% & above	15% & above	4%
Vitality	----	75% & above	50 % & above	58% & above

Table 1. WHO reference values over the years.

Like all other biological parameters, semen parameters also vary hugely from time to time in the same individual. The huge variation in a man's semen parameters over time is beautifully depicted in the enclosed figure (Fig 1). However unlike other biological parameters, there is no lower limit (below which pregnancy is not possible) or there is no upper limit above which pregnancy is always possible. With no definable lower or upper limit, semen analysis seems to be a numbers game.

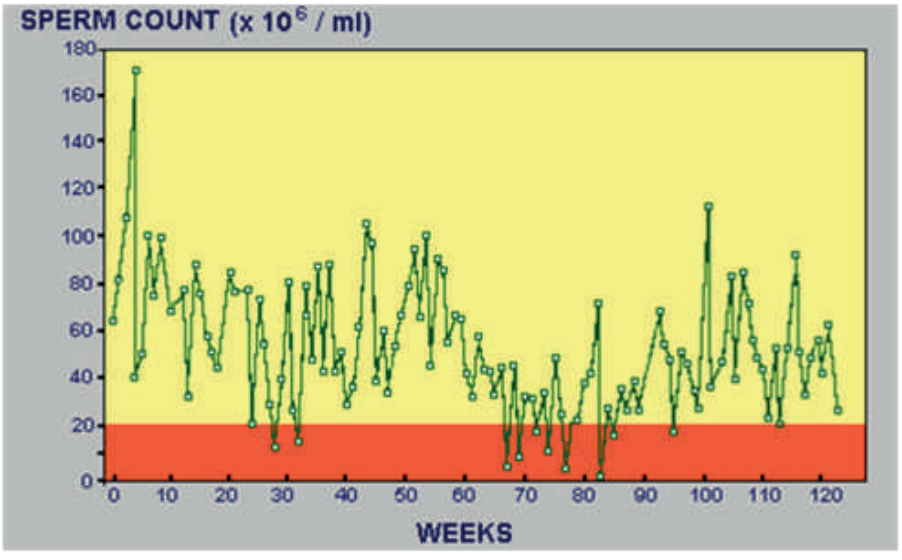


Fig 1. Variation in sperm concentration over time in a single individual (from WHO)

The spermatozoa concentration which varies hugely looks more like the stock market fluctuation. This variation not understood by the patients and the treating physicians, causes lots of anxiety and concerns for the patients and the physicians. We have also observed that the other semen variables like motility and morphology vary from time to time in the same individual (Fig 2).

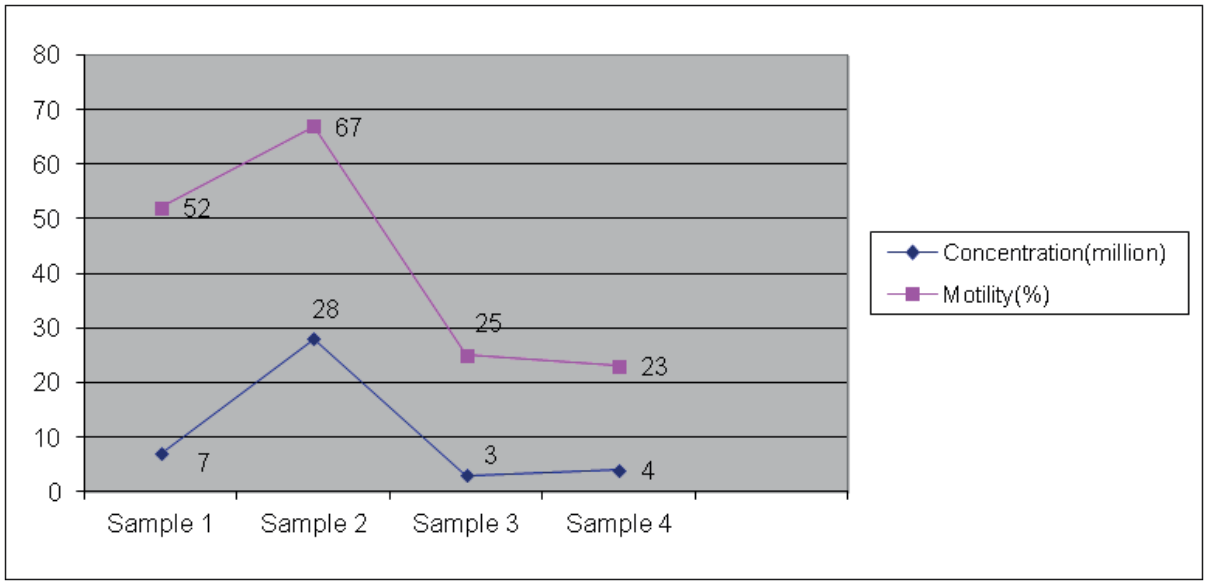


Fig 2. Variation in sperm concentration and motility over time

The fertility is the sum total of two peoples fertility as opposed to one person's alone. Therefore the values of one person's semen parameters is of little significance except in the extremes as when the sample is azoospermic or totally asthenozoospermic or totally necrozoospermic. Total asthenozoospermia and total necrozoospermia are very rare conditions. Many men have been subjected to the several forms of medical therapy and surgical therapy such as varicocoelectomy based on previous WHO semen parameters. Therefore it is possible that men may have been subjected to unnecessary medical/surgical treatment as a consequence of potentially inaccurate diagnostic criteria.

Today we suggest that semen parameters need to be redefined for the individual population. We propose that after decades of experience from full time infertility work that, even today, semen analysis remains largely subjective and not as objective as it needs to be. We have been dealing with parameters such as volume, concentration, motility & morphology without knowing what is "normal". Doubts have been raised about the value of sperm counting more than 100 years back. In 1910, Benedict said "Enumeration of spermatozoa has seldom been practised. How useful either as an index of sexual or general health it is, is not yet known".[2]

The time is now ripe for us to carefully rethink and redefine normal semen parameters. Population based studies are essential to establish normal values. While WHO manual 5th edition may be a good starting point, it still needs further definition for each population.

References:

1) Van Leeuwenhoek A. Letter to Oldenburg dated 9 October 1676, Philosophical Transactions 1677; 12: 831.

2) Benedict. A. L. : Enumeration of Spermatozoids. N. Y. Med.Journ., 91, p. 1169, 1910.

3) Macomber, D,- Sanders, M B. - The Spermatozoa Count - N Engl J Med 1929; 200:981-984

4) World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen, 5th ed. Geneva: World Health Organization; 2010.

Original Article

Normal and Abnormal Oocytes Observed During Assisted Reproductive Technique (ART) Procedures

Dr.P.Savitha*, Dr.D.Ramesh Raja*, Dr.Radha Pandiyan**

Chettinad Health City Medical Journal 2012; 1(1): 4 - 11

Dr.P.Savitha, B.D.S., D.C.E., Clinical Embryologist, Department of Reproductive Medicine. Completed Bachelor of Dental Surgery in the year 2004. Did Post Graduate Diploma in Clinical Embryology in Chettinad University in the year 2008 and joined as Embryologist in Chettinad Super Specialty hospital. Attended hands on work shop at Chennai in 2010 for vitrification and at Delhi in 2011 for IMSI (Intracytoplasmic Morphologically Selected sperm Injection) and micromanipulation techniques.

*Clinical Embryologist, CSSH, **Senior Consultant in Reproductive Medicine, CSSH (Chettinad Super Speciality Hospital).

Abstract

A competent human MII (Metaphase II) oocyte is regarded as crucial for efficiency of assisted reproductive technique (ART). The non invasive morphological appearance of the oocyte helps in evaluation of developmental competency of oocyte. The purpose of this observational study was to document different patterns of oocyte morphology in our IVF laboratory. This study includes 121 patients who underwent ART from January 2011 to December 2011. The results showed that there were a considerable number of normal and abnormal oocytes observed during ART cycles. From the morphological features of 1070 oocytes retrieved from 121 ART patients, 311(29.06%) oocytes were abnormal. Of 121 patients, oocytes retrieved from 90 patients (74.28%) had one of the abnormalities. Most common abnormality observed were empty and broken zona which were found in 57 oocytes (18.3%) and fragmented polar body which were found in 49 oocytes (15.7%). Of the 90 patients who showed oocyte abnormalities, oocytes from 61 patients (67%) showed either of the two abnormalities mentioned above. We find 74.28% of our patients out of 121 patients had one of the abnormalities. This can be due to underlying infertility, effect of ovarian hyper stimulation or advanced maternal age. Further work is required to assess the benefits of oocyte assessment in selecting best embryo for transfer.

Key Words: Assisted Reproduction, normal and abnormal oocytes

Introduction

Human reproduction is the result of union of two highly specialized cells- the oocyte and the spermatozoon. Of these, the oocyte deserves special mention because of its key functions; it receives the spermatozoon during fertilization, contributes the majority of the cytoplasm for early embryo development and provides half of the genome for one the resulting zygote. In lower animals, it provides information to initiate the events of early embryo development.

Important changes take place in the nucleus and cytoplasmic components of the oocyte at maturation, in preparation for fertilization i.e.

1. Unequal cell division by the oocyte, retaining the haploid set of chromosomes and major portion of cytoplasmic organelles.
2. Exclusion of small sized 1st polar body with remaining chromosomes.
3. Cumulus expansion around various layers of cells surrounding the oocyte.

These intracellular and extracellular components are critical for the survival and fertilization of oocyte. Proper evaluation of nuclear and cytoplasmic maturation of human oocytes is extremely important for the result of In Vitro Fertilization. Low quality oocytes are unlikely to fertilize or will not be competent to produce good embryos. One third of the collected oocytes during IVF may show at least one morphologic anomaly that could negatively influence the embryo development. This paper aims to investigate different patterns of oocyte morphology we encountered in our IVF laboratory.

Methodology:

Data collection

In this observational study the data were collected from the records of all sub-fertile couples who attended the IVF centre at the Department of Reproductive Medicine, Chettinad Health City, from January 2011 to December 2011. Data from 121 patients who underwent assisted reproductive technique (ART) were included in the study. All women were less than 40 years. In all patients, controlled ovarian hyperstimulation was carried out with urinary follicle stimulating hormone (FSH, i.m.). The ovarian response was monitored by serial transvaginal ultrasound followed by the injection of 10,000 IU of human chorionic gonadotrophin (hCG, i.m.). Transvaginal ultrasound-guided oocyte retrieval was performed about 35hours post hCG injection.

Oocyte evaluation

The morphological feature of each oocyte was evaluated with the aid of an inverted microscope.

The oocytes were classified as follows

A. normal oocytes

B. oocytes with intracytoplasmic abnormalities

C. oocytes with extracytoplasmic abnormalities

D. oocytes with abnormal shape

Results:

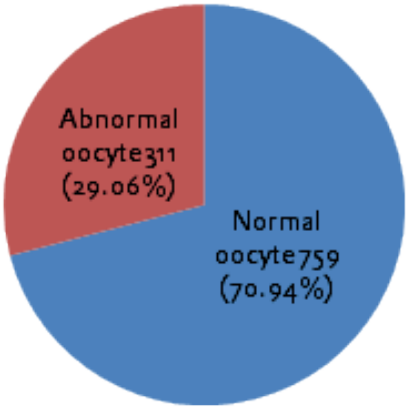
The results showed that there were a considerable number of normal and abnormal oocytes observed during ART cycles. Table 1 demonstrates the morphological features of 1070 oocytes retrieved from 121 ART patients, of which 311(29.06%) oocytes were abnormal. Of 121 patients, oocytes retrieved from 90 patients (74.28%) had one of the abnormalities mentioned in Table 1. Pie chart 1 shows the percentage of abnormal oocytes retrieved and the pie chart 2 shows the percentage of different types of oocyte abnormalities from retrieved oocytes.

Table -1 Different forms of oocyte abnormalities observed during our ART procedure.

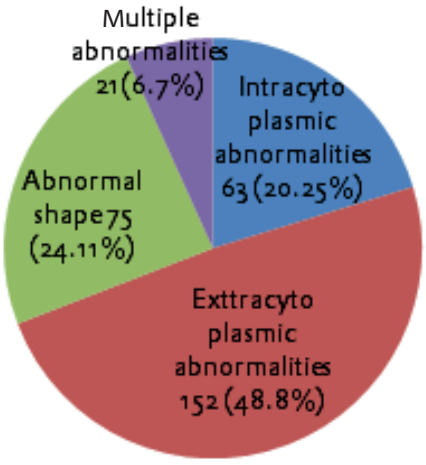
s.no	Forms of Oocyte abnormalities	Total number of oocytes with abnormalities	Total number of patients with oocyte abnormalities
	Intracytoplasmic abnormalities		
1.	Vacuolated	23(7.3%)	17(18.8%)
2.	Abnormal texture	31(9.9%)	11(12.2%)
3.	Degenerated	8(2.5%)	7(7.7%)
4.	Parthenogenetic oocyte	1(0.3%)	1(1.1%)
	Extracytoplasmic abnormalities		
5.	Debris in PVS	39(12.5%)	8(8.8%)
6.	Large PVS	19(6.1)%	12(13.3%)
7.	Fragmented polar body	49(15.7%)	26(28.8%)
8.	Big polar body	1(0.3%)	1(1.1%)
9.	Thick zona	33(10.6%)	5(5.5%)
10.	Thin zona	11(3.5%)	3(3.3%)
	Abnormal shaped oocyte		
11.	Empty zona	57(18.3%)	35(38.8%)
12.	Zona free	5(1.6%)	5(5.5%)
13.	Irregular shape	11(3.5%)	8(8.8%)
14.	Giant oocyte	1(0.3%)	1(1.1%)
15.	Small oocyte	1(0.3%)	1(1.1%)
16.	**Multiple abnormalities**	**21(6.7%)**	**9(10.0%)**
	Total	**311(29.06%)**	**90(74.28%)**

PVS - perivitilline space, **Abnormal texture** - dark and granular, **Parthenogenetic oocyte** - a form of asexual reproduction means development of an embryo from an unfertilized egg cell, **thin zona** - ≤10 µm thickness, **thick zona** - ≥ 22 µm thickness.

Serial no 1-4 from the table shows total of 63 oocytes with Intracytoplasmic abnormalities (20.25%) from 36 patients (40.0%). Serial no 5-10 from the table shows total of 152 oocytes with Extracytoplasmic abnormalities (48.8%) from 55 patients (61.1%). Serial no 11-15 from the table shows total of 75 oocytes with abnormal shape (24.11%) from 50 patients (55.5%). Serial no 16 from the table shows 21 oocytes with multiple abnormalities (6.7%) from 9 patients (10.0%)



Pie chart 1. Percentage of abnormal oocytes retrieved



Pie chart 2. Percentage of different types of oocyte abnormalities from retrieved oocytes

Most common abnormalies observed were empty and broken zona which were found in 57 oocytes (18.3%) and fragmented polar body which were found in 49 oocytes (15.7%). Of the 90 patients who showed oocyte abnormalities, oocytes from 61 patients (67%) showed either of the two abnormalities mentioned above. This means 67% of patient in our ART programme have oocytes with an empty and broken zona or fragmented polar body. All types of abnormal oocytes we observed are shown in the following figures. Figures 1 & 2 show normal oocytes. Figures 3- 8 show oocytes observed with extracytoplasmic abnormalities. oocytes with intracytoplasmic abnormalities are shown in figures 9- 18. Abnormal shaped oocytes are shown in figures 19- 26.

Normal human oocyte

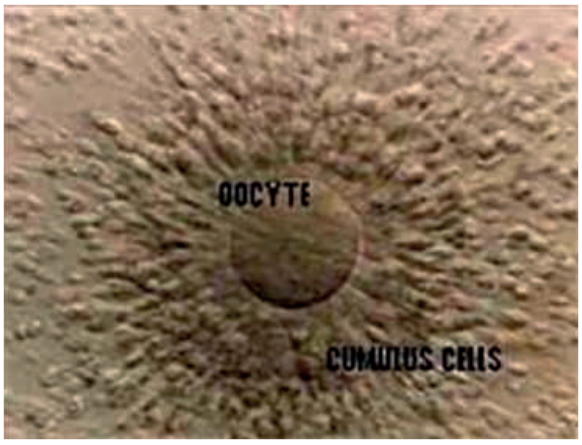


Fig 1. Oocyte with cumulus corona complex

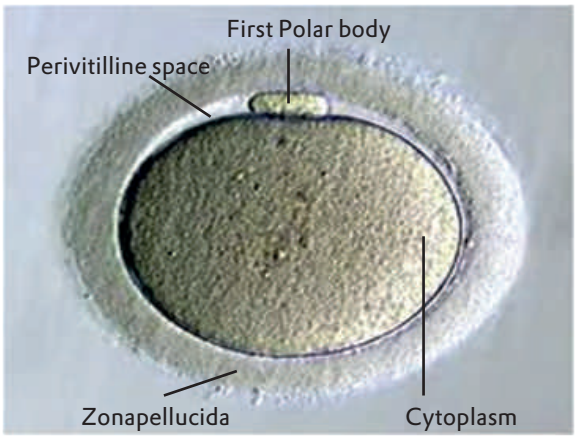


Fig 2. Normal mature Metaphase two human oocyte after cumulus removal

Abnormal human oocytes
Extracytoplasmic abnormalities:

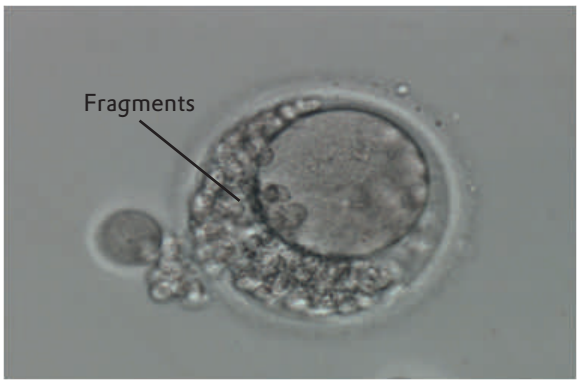


Fig 3. Fragments in PVS.

Fig 4. Thin zona

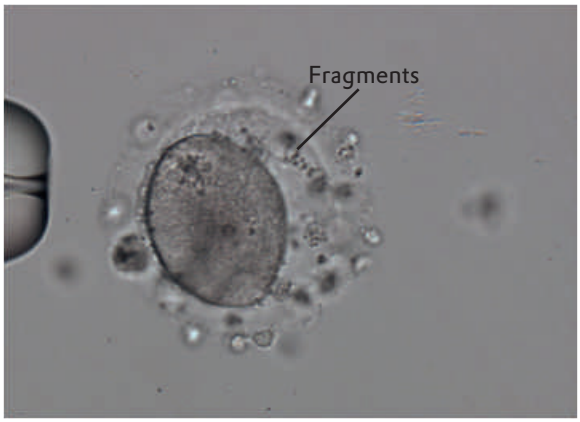


Fig 5. Metaphase one oocyte-Fragments in PVS

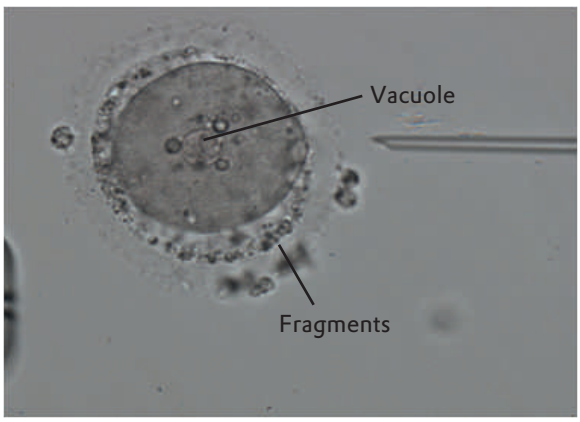


Fig 6. Metaphase one Oocyte- Fragments in PVS with central vacuole

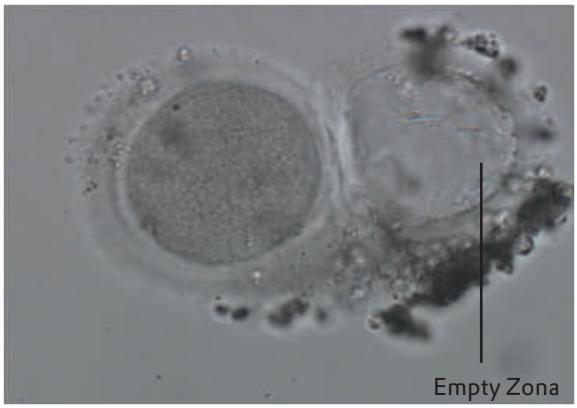


Fig 7. Extra empty zona

Fig 8. Big polar body

Intracytoplasmic abnormalities

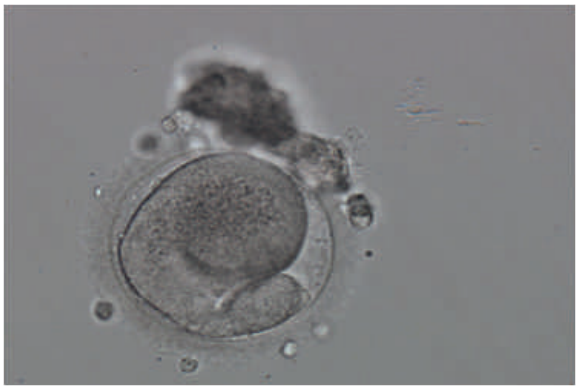


Fig 9. Abnormal shaped cytoplasm

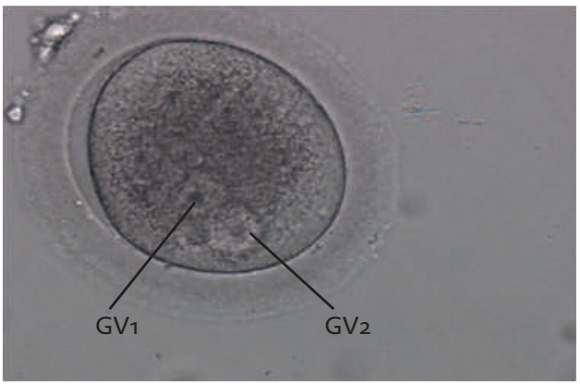


Fig 10. Central granularity with two germinal vesicles

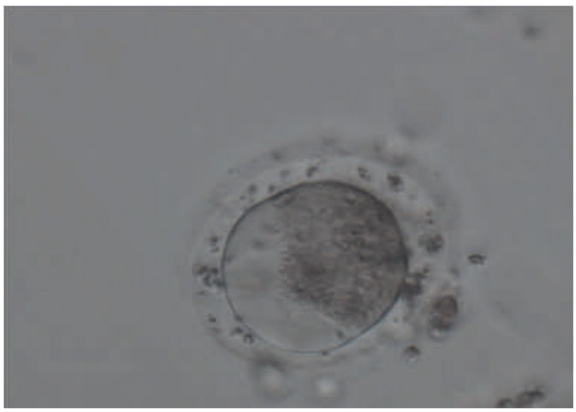


Fig 11. Abnormal textured cytoplasm

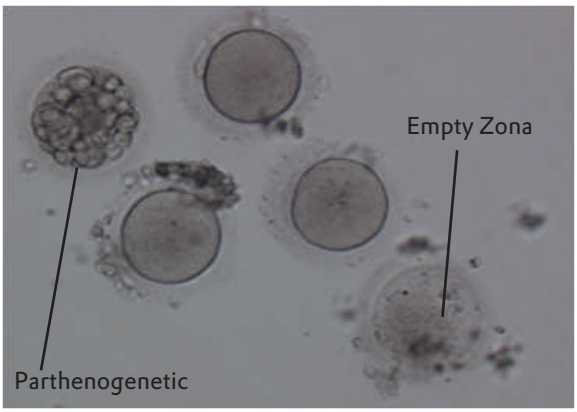


Fig 12. Parthenogenetic oocyte and empty zona

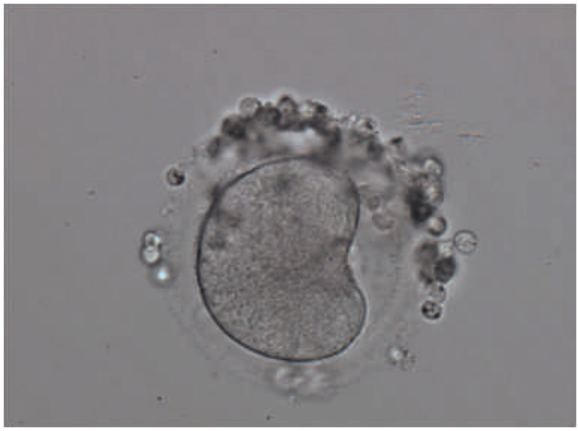


Fig 13. Abnormal shaped oocyte cytoplasm

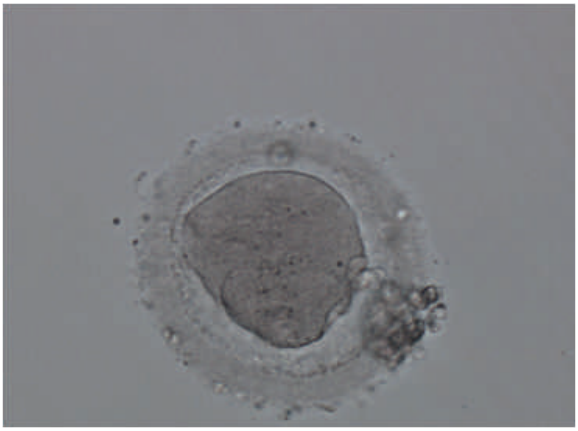


Fig 14. Abnormal shape and textured cytoplasm

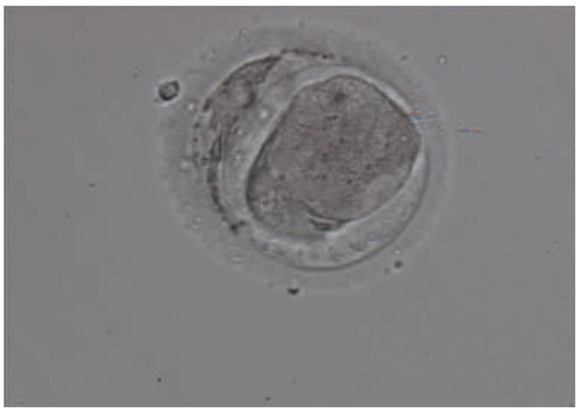


Fig 15. Abnormal shaped cytoplasm

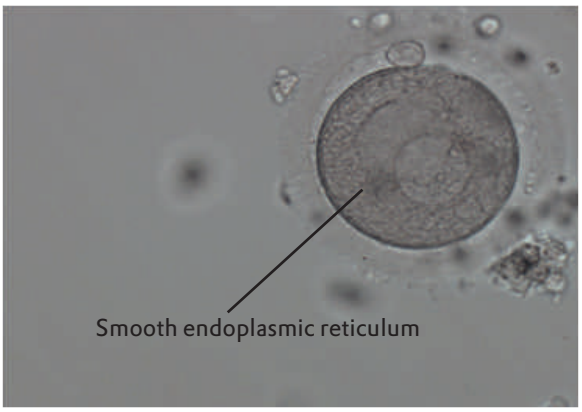


Fig 16. Smooth endoplasmic reticulum aggregation

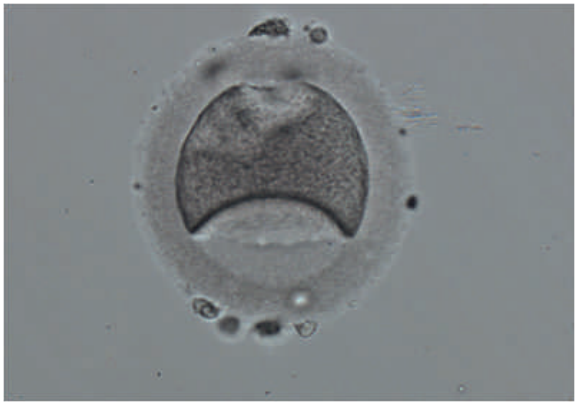


Fig 17. Crescent shaped cytoplasm

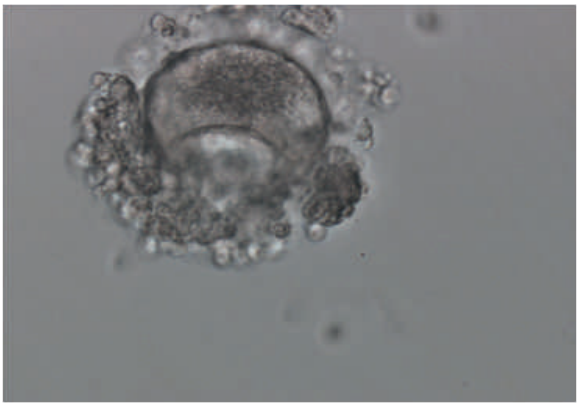


Fig 18. Abnormal cytoplasm with tight corona cells

Abnormal shape

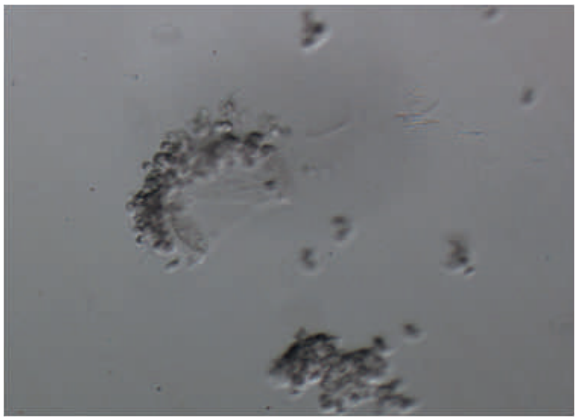


Fig 19. Broken zona

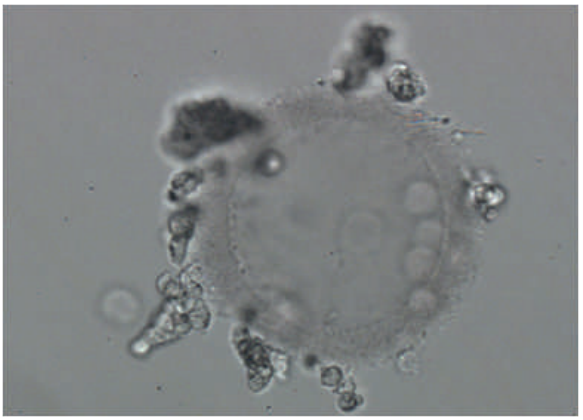


Fig 20. Empty zona

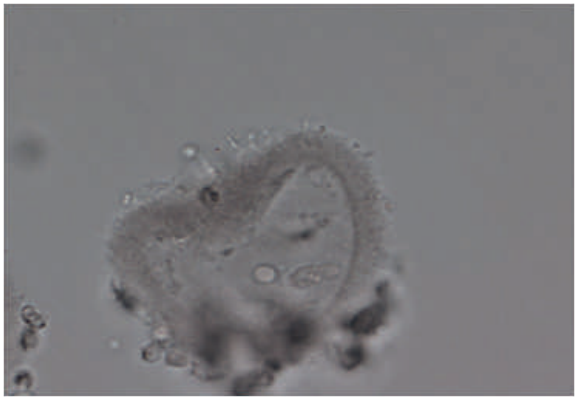


Fig 21. Heart shaped empty zona

Fig 22. Giant empty zona

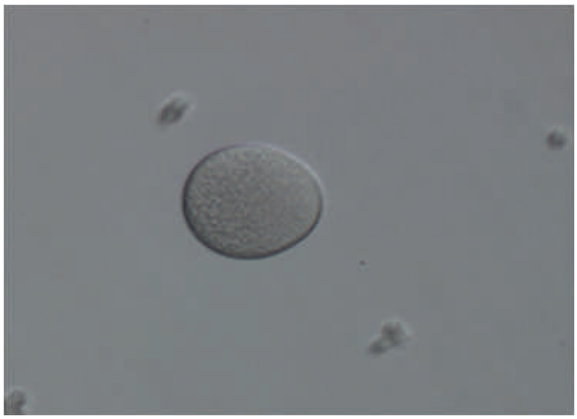


Fig 23. Zona free oocyte cytoplasm

Fig 24. Giant oocyte

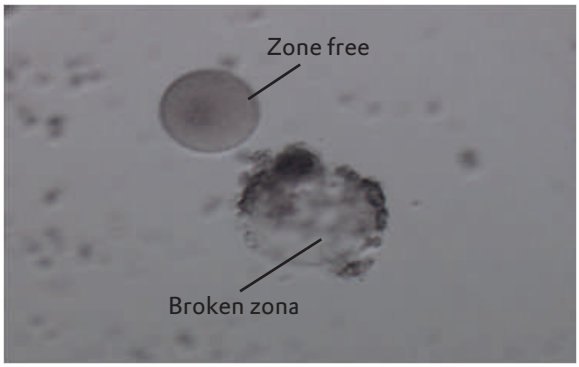


Fig 25. Broken zona with zona free cytoplasm

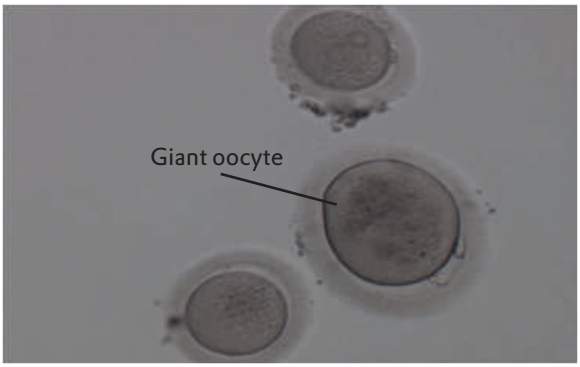


Fig 26. Giant oocyte

Discussion:

An oocyte is considered normal if it is spherical in shape and is enclosed by a uniform zona pellucida, with a uniform translucent cytoplasm free of inclusions and a size-appropriate polar body.

Nuclear Maturation

Polar body (PB): The first polar body is the marker of nuclear maturation. An oocyte with 1st polar body (Metaphase II) is at a stage in meiosis, when it is receptive to fertilisation for a period of 12-24 hours.The first polar body in human remains intact for more than 20 hr afte ovulation, while in mammals it has a shorter life. We can postulate that the first polar body morphology gives information not only on the nuclear maturation of the oocytes but on the age of the oocyte also.

Oocyte abnormalities

Ebner suggests classifying oocyte anomalies as intracytoplasmic and extracytoplasmic (Ebner T. 2001)[1]. He suggested that more than a half of the collected oocytes will show at least one anomaly. In our study, however we found that 29.06% of the oocytes collected were abnormal. The below table-2 shows the different forms of oocyte abnormalities.

Table 2. Different forms of oocyte abnormalities

Intracytoplasmic abnormalities	Extracytoplasmic abnormalities	Abnormal Oocyte shape
1.Variations in colour or granularity of the cytoplasm	1.Wide perivitelline space size	1.Giant oocyte
2.Presence of inclusions, vacuoles or retractable bodies (Ebner et al. 2003,)[2]	2.Perivitelline space granularity	2.Small oocyte
3.Aggregations of the smooth endoplasmic reticulum (Otsuki J. 2004)[3]	3.Fragmented, multiple and big first polar body	3.Zona free
4.Parthenogenetic	4.Anomalies in Zona pellucida layer- thick, thin and abnormal shape	4.Empty zona
		5.Oval or irregular shape

In our study the most commonly found oocyte abnormalities were empty and broken zona. These were found in 57 oocytes which contributes 18.3% of the total 311 abnormal oocytes. These oocytes were found to have no cytoplasm and cannot be used for ART procedure. Loutradis et al., (1999)[4] reported from his study that drastic morphological alterations (broken or empty zona pellucidae) were regarded as unsuitable for ICSI.

The second most common oocyte abnormality was found to be fragmented polar body in 49 oocytes (15.7%) from total of 311 abnormal oocytes. However De Santis et al. (2005)[5] did not find any correlation between surface characteristics, fragmentation and fertilization rate, embryo quality and blastocyst formation and Ten et al. (2007)[6] found fertilization rates and embryo quality were not related to the shape (normal, fragmented or irregular) of first polar body. In contrast to these observations, Ebner et al. (2000)[7] found a strong correlation between all observed morphological features of first polar body (intact versus rough surface, fragmented or enlarged) and fertilization rates/embryo quality.

Embryos developing from giant oocytes were reported to have increased chance for (Digynic Triploidy) (Digynic Triploidy is the result of fertilization of a diploid ovum by a single sperm, with the diploid ovum being the result of either an error in the first (MI) or second (MII) meiotic division). This is in spite of the normal in vitro development as reported by Rosenbusch et al and Balakieretal (2002)[8,9].

According to a review by Laura Rienzi et al[10], out of the 92 studies of different parameters (including both single features and cumulative scores) investigating direct association of oocyte morphology with the further embryo prognosis, 57 studies resulted in a significant correlation with good embryo outcome, whereas in 35 studies no predictive value of the microscopic feature was found and the diversity of observations and results did not allow statistical comparison. However, there was no clear tendency of improved accuracy regarding the predictive value in recent publications compared with the earlier ones. 24 of 42 study observations performed between 1997 and 2005 have found correlations with the embryo outcome, while 33 out of 50 studies between 2006 and 2009 found correlations.

However we suggest degenerated, parthenogenetic, giant oocytes, empty or broken zona and some forms of oocytes with multiple oocytes (abnormal shaped with granular cytoplasm) should be considered unsuitable for ICSI.

We found 90 (74.28%) of our patients out of 121 patients had one or more oocyte abnormalities.

This can be due the following reasons

1. Underlying infertility
2. Effect of ovarian hyper stimulation
3. Advanced maternal age

Conclusion:

From the above discussion it is clear that there have been numerous studies, which have attempted to correlate oocyte morphology with embryo developmental competency. There is no consensus, with some studies supporting some relationship with oocyte abnormalities and compromised embryo development and, in contrast, some studies which do support an association with implantation potential and oocyte abnormalities. To date there are too many confounding factors in the various papers, which have been reviewed in part by Rienz et al., (2011)[10].

The morphological evaluation of oocytes and its impact on embryo quality has been controversial. However, abnormal oocyte morphology can be directly influenced by the follicular environment, ovarian function and the effects of ovarian hyper stimulation used in assisted reproductive technology. Furthermore, 70.94 % of morphologically normal oocytes can give rise to a small percentage of pregnancies, while morphological abnormalities appear to be associated with compromised oocyte quality, their precise identification and impact on embryo development is currently lacking, suggesting that most of the problems leading to poor embryonic development and implantation failure cannot be detected using standard microscopic evaluation. Further work is therefore required to assess both the morphological characteristics as related to oocyte developmental competence and the cellular and molecular findings of the oocyte for understanding the pathophysiology, will help design strategies to improve fertilization and embryo development.

Acknowledgements

We gratefully acknowledge the help and guidance from Dr.N.Pandiyan; comments and helpful discussions from Dr. Thilaka Muthiah and Dr.G.Kavitha for her support.

REFERENCE

1) Ebner,T., Yaman,I.,Mosser,M.etal. Prognostic value of first polar body morphology on fertilization rate and embryo quality in intracytoplasmic sperm injection. Hum Reprod 2000;15:427-430.

2) Ebner T, Moser M, Sommergruber M, Puchner M, Wiesinger R, Tews Developmental competence of oocytes showing increased cytoplasmic viscosity. Hum Reprod 2003;18:1294–1298.

3) Otsuki J, Okada A, Morimoto K, Nagai Y, Kubo H. The relationship between pregnancy outcome and smooth endoplasmic reticulum clusters in MII human oocytes. Hum Reprod 2004;19:1591–1597.

4) Loutradis,d.,Drakakis,P,Kallianidis,K.etal. Oocyte morphology correlates with embryo quality and pregnancy rate after intra cytoplasmic sperm injection. Fertil.steril1999;72: 240-244.

5) De Santis L, Cino I, Rabellotti E, Calzi F, Persico P, Borini A, Coticchio G. Polar body morphology and spindle imaging as predictors of oocyte quality. Reprod Biomed Online 2005;11:36–42.

6) Ten J, Mendiola J, Vioque J, de JJ, Bernabeu R. Donor oocyte dysmorphisms and their influence on fertilization and embryo quality. Reprod Biomed Online 2007;14:40–48.

37 Ebner T, Yaman C, Moser M, Sommergruber M, Feichtinger O, Tews G. Prognostic value of first polar body morphology on fertilization rate and embryo quality in intracytoplasmic sperm injection. Hum Reprod 2000;15:427–430.

8) Rosenbusch B, Schneider M, Glaser B, Brucker C. Cytogenetic analysis of giant oocytes and zygotes to assess their relevance for the development of digynic triploidy. Hum Reprod 2002;17:2388–2393.

9) Balakier H, Bouman D, Sojecki A, Librach C, Squire JA. Morphological and cytogenetic analysis of human giant oocytes and giant embryos. Hum Reprod 2002;17:2394–2401.

10) Laura Rienz, Gabor Vajta and Filippo Ubaldi. Predictive value of oocyte morphology in human IVF: a systematic review of the literature. Human Reproduction Update 2011; 17: 34–45,

GIRLS SHOULD REMAIN SLIM & TRIM EVEN AT BIRTH

In a cohort study carried out on 1053 seventeen - year olds, Rae-Chi Huang and his associates of The University of Western Australia found that those women, who were heavier at birth, were at a greater risk of developing diabetes and related metabolic risks. At seventeen years, these women were found to have greater waist circumference, higher levels of triglycerides and insulin, and lower HDL-cholesterol (good cholesterol). However, similar association between birth weight and the metabolic risk was not observed in males. These findings are particularly significant taking into consideration increasing incidence of maternal obesity and gestational diabetes. The latter means that there will be rise in heavier female newborns. The results of this study have been accepted for publication in The Endocrine Society's Journal of Clinical Endocrinology and Metabolism (JCEM). In related medical news, a controversial study has been undertaken in Britain to enable pregnant women to deliver slim babies

(http://www.medindia.net/healthnews/Women-Child-Health-News.asp)

- Dr. K. Ramesh Rao

House boat - Kerala

Review Article

Inflammation in Acute Coronary Syndrome

Dr.M.Chokkalingam, Counsultant, Interventional Cardiologist, Chettinad Super Speciality Hospital

Chettinad Health City Medical Journal 2012; 1(1): 12 - 18

Dr M.Chokkalingam did his undergraduation and postgraduation in Internal Medicine from Madurai Medical College. Further he did his DNB course from the renowned Dr.KM Cherian's Heart Foundation. He is a gold medalist during his postgraduation. Currently he is working as Consultant and Interventional Cardiologist at Chettinad Superspeciality Hospital. His areas of interest include preventive cardiology and interventional cardiology.

Abstract

This article reviews the role of inflammation in coronary artery disease, particularly its conversion from a chronic to an acute illness. An overview is provided about various inflammatory markers and their role in inflammation which lead to the development and progression of atherosclerotic vascular disease and its clinical consequences, especially acute coronary syndromes. The very episodic nature and the common short duration of acute coronary syndromes suggest the role of inflammatory stimuli. Causes of inflammation may be multiple and not necessarily the same in all patients, and their effect is probably modulated by the individual immunological and inflammatory response.

Key Words: Atherosclerosis, Coronary inflammation, Thrombosis, Vasoconstriction.

Introduction

Inflammation is becoming an intriguing focus of research as a possible pathogenetic component and therapeutic target in ischemic heart disease. However, the potential links between inflammation and ischemic heart disease are present at three levels at least. First, the inflammatory response has been known for many years to play a major role in schaemia/reperfusion injury, and its reduction can limit myocardial damage[1]. Second, inflammation is a very common feature of the chronic atherosclerotic process, as first described by Virchow in 1856[2] and recently comprehensively reviewed by Ross[3]. Finally, inflammation may be an acute pathogenetic component of instability in approximately half of patients with acute coronary syndromes (ACS), independently of the atherosclerotic and ischaemic burdens[4].

There may be several actual triggers of inflammation. The inflammatory response may influence prognosis through modulating the consequences of ischemia and necrosis in some individuals, through sudden development of instability, or through atherogenesis in others. The present review focuses on the independent role of inflammation in ACS.

The final common pathway through which instability precipitates ACS is represented by a variable combination of coronary thrombosis and vasoconstriction in epicardial arteries and in resistive coronary vessels, superimposed on a variable atherosclerotic background[5]. Thrombosis is the most obvious acute component, spasm and vasoconstriction are transient,however, and can only be detected by chance, when critical stenoses are relieved by nitrates[6], or by design, when provocative tests are used[7,8]; coronary microvascular constriction can only be inferred by special studies[9].

A substantial percentage of patients do not respond sufficiently to thrombolytic, anticoagulant and antiplatelet agents. Moreover, at 4–6 months after hospital discharge, patients with ACS in the aggressive arms of interventional[10] and medical trials[11] still have a 9–12% incidence of major cardiac events. Thus, only a clearer understanding of the actual triggers of instability could lead to major improvements in therapeutic efficacy.

Elevated inflammatory markers associated with adverse prognosis

Elevated values of circulating inflammatory markers, such as CRP, serum amyloid A protein, interleukin-6 (IL- 6) and interleukin-1 (IL- 1) receptor antagonist, are commonly found in ACS. Such elevation is associated with in-hospital and short-term adverse prognosis[12–19], and may reflect a primary inflammatory trigger of coronary instability.

The contribution of each of these secondary and primary mechanisms of inflammation to prognosis may vary in different groups of patients according to the criteria used for their selection. In turn, the short-term prognostic role of elevated CRP levels in ACS may be at least partly correlated with the long-term prognostic role of CRP levels within the normal range in normal individuals[20,21] and with that of elevated levels in chronic coronary disease[22].

C-Reactive Protein (CRP)

CRP is the inflammatory marker receiving the most attention to date. It is an acute phase reactant normally present in plasma at low levels, and increases > 100-fold in response to inflammatory stimuli. It is produced by hepatocytes in response to stimulation by IL-6. It is also produced by human coronary artery smooth muscle

cells.[23] Although initially considered only a "marker" of inflammation, CRP itself has been shown to possess proinflammatory and proatherogenic properties. It stimulates endothelial cells to express adhesion molecules and secrete cytokines[24,25] and it decreases the expression of endothelial NO (Nitric Oxide) synthase.[26] CRP accumulates in macrophage-rich regions of nascent atherosclerotic lesions and activates the macrophages to express cytokines and tissue factor, while enhancing macrophage uptake of LDL (Low Density Lipoproteins).[27] It also amplifies proinflammatory effects of several other mediators including endotoxin.[28,29] In a post mortem study of 302 autopsies of men and women with atherosclerosis, median CRP levels were higher with acute plaque rupture than in stable plaques or controls.[30] The levels correlated with the staining intensity for CRP in macrophages and the lipid core of plaques, and it increased with the number of thin cap atheromas found in coronary arteries.

Plasma CRP levels at the upper end of the reference range in apparently healthy men and women, in the absence of other sources of inflammation, correlated with increased risk of future cardiovascular events, including myocardial infarction (MI), peripheral vascular disease with claudication and stroke.[31] These data support the view that systemic CRP accurately reflects the number of vulnerable atherosclerotic plaques.

Unfortunately, many other factors affect CRP. For example, CRP levels are related to abdominal obesity.[32] They are elevated in patients with metabolic syndrome and type 2 diabetes, and CRP levels correlate with the severity of the glycemic state and insulin resistance.[33–35] In a German health and nutrition survey, there was an almost linear relation between the number of components of the metabolic syndrome and median CRP concentrations.[36] Cigarette smoking is the strongest environmental stimulus for CRP production. Current smokers usually have 2-fold higher concentration of both fibrinogen and CRP compared with those who never smoked. Hormone replacement therapy (HRT) raises CRP, and levels were 2 times higher in 493 healthy post-menopausal women in the Women's Health Study who were taking HRT than among women not taking HRT. The difference was present in all subgroups, including those with no history of hypertension, hyperlipidemia, obesity, diabetes, cigarette consumption or a family history of premature coronary artery disease[37]. Renal insufficiency (serum creatinine > 1.3 mg/dl in women and > 1.5 mg/dl in men) was independently associated with elevations in CRP, which may explain in part the increased cardiovascular risk in patients with kidney disease[38].

Myocardial necrosis and ischaemia

The first demonstration that elevated CRP is correlated with adverse short-term prognosis, independently of necrosis and ischaemia, was provided by Liuzzo et al[13]. Thoseinvestigators studied selected patients with unstable angina, in Braunwald class IIIB, who had no evidence of myocardial necrosis and an ischaemic burden similar to that of necrosis and an ischaemic burden similar to that of patients without CRP elevation. Those findings were subsequently corroborated by the observed absence of CRP elevation in patients with variant angina and large ischaemic burden[39] and by the persistence of elevated CRP values in 50% of unstable patients after discharge, which were associated with recurrent episodes of instability and infarction[16]. The in-hospital and short-term prognostic value of elevated CRP level, independently of necrosis, ischaemia and atherosclerosis, suggests that inflammation may play a primary pathogenetic role in the development of instability in at least some patients with ACS.

Cytokines

IL-6 (an interleukin) is the major cytokine of the acute phase response and is intimately involved in the pathogenesis of ACS[40] It stimulates production of fibrinogen and CRP, triggers the expression of adhesion molecules and TNF (Tumour Necrosis Factor), stimulates macrophages to produce tissue factor and MMPs, and stimulates vascular smooth muscle cell proliferation and platelet aggregation.

Data from the FRISC-II study group found that circulating levels of IL-6 are a strong independent marker of increased mortality among patients with unstable angina and may be useful in directing subsequent care[41] As seen with other markers of increased risk, an early invasive strategy led to a 65% relative reduction in 1-year mortality among patients with elevated IL-6 levels. By contrast, among those with low IL-6 levels (i.e., lower risk), an early invasive strategy did not confer any significant benefit over a noninvasive strategy.

Furthermore, among patients randomized to the non-invasive arm, the risk associated with elevated IL-6 levels was markedly attenuated if they were assigned to therapy with dalteparin rather than placebo.[42]

TNF-a is a cytokine produced by a variety of cells, including macrophages, endothelial cells and smooth muscle cells. It has an essential role in the amplification of the inflammatory cascade. High levels of TNF- identify stable patients with CAD at risk for recurrent cardiovascular events[43,] but its short plasma half-life has limited its clinical utility as a screening tool.

CD40 Ligand

CD40L is a transmembrane protein that is structurally related to TNF- . Soluble CD40L (sCD40L) is released from both stimulated lymphocytes and activated platelets.

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)

The West of Scotland study group reported that baseline levels of Lp-PLA2 were a strong independent predictor for incident coronary heart disease in a cohort of high-risk hyperlipidemic men.[44] The results showed that those with the highest levels of Lp-PLA2 had twice the risk of an event compared to those with

the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators, including CRP.

Elevated PLA2 has also been associated with increased risk of cardiovascular events in women.[45] The Atherosclerosis Risk in Communities (ARIC) study showed that elevated levels of Lp-PLA2 are higher in incident coronary disease cases. In individuals without elevated LDL levels (i.e., < 130 mg/dl), Lp-PLA2 levels were independently associated with coronary disease, even after adjustment for traditional risk factors and CRP.[46]

Matrix Metalloproteinases (MMPs)

MMPs are a family of enzymes involved in the focal destruction of extracellular matrix. Recent findings have revealed enhanced expression of MMP in the shoulder regions of plaque at sites where fissuring is commonly observed. This renders plaque more susceptible to mechanical stresses and therefore more vulnerable to rupture.

Inflammatory mediators, such as TNF- , CD40L and IL-1, upregulate MMP activity in macrophages and this interaction may represent a link between inflammation and plaque degeneration. Circulating MMP-1, -2 and -9 were elevated on admission in patients with acute MI and unstable angina, and high levels of MMP-9 were identified in atherectomy specimens from patients with recent plaque rupture.[47–51] .

Cellular Adhesion Molecules

In the ARIC study, subjects in the highest quartile for ICAM-1 had more than 5 times the risk for incident coronary heart disease or carotid atherosclerosis compared with subjects in the lowest quartile, even after adjustment for other risk factors. The findings from ARIC were confirmed in the Physicians' Health Study,[52] in which relative risk for MI was 1.6 in men with circulating or soluble ICAM-1 in the highest quartile compared with the lowest. This association persisted after adjusting for other risk factors, and in multivariate analyses, the risk for MI was 80% higher in men with sICAM-1 in the highest quartile.

Prevalence of inflammation

In patients with ACS the prevalence of a primary inflammatory pathogenetic component of coronary instability, as detected by elevated CRP level, varies considerably. Elevated CRP (above 3 mg . l – 1) is found in fewer than 10% of normal individuals and in fewer than 20% of patients with chronic stable or variant angina.However, elevated CRP is found in more than 65% of patients with unstable angina and Braunwald class IIIB, and in more 90% of patients with acute infarction preceded by unstable angina, but in fewer than 50% of those in whom the infarction was totally unheralded (in samples taken before elevation of markers of necrosis)[13,19,53].

The absence of elevated CRP in over 30% of patients with severe unstable angina and in over 50% of those with acute myocardial infarction not preceded by unstable angina suggests that inflammation may not be the trigger of coronary instability in all patients.

Chronic inflammatory component of atherosclerosis

Angiographic studies show that the severity and extension of coronary atherosclerosis is significantly less in patients who first present with infarction or unstable angina than in those who first present with chronic stable angina[54,55]. Moreover, the results of the International Pooling Project show that, in approximately half of the individuals older than 50 years who died from non-cardiac causes, about 50% of the coronary intima is covered by raised fibrous plaque.

Inflammatory stimuli

None of the putative inflammatory stimuli, either infectious (e.g. Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus) or non-infectious (e.g. oxidized lowdensity lipoprotein, homocystein and toxins), appear to be a sufficiently prevalent cause of instability[16,56–61]. The incidence of seropositivity for infectious agents in patients with ACS is higher than that in control individuals, but is not significantly different from that found in patients with chronic stable coronary disease,and some patients with ACS are seronegative.

Finally, seropositivity for infectious agents does not correlate with elevated levels of CRP[16].A more likely inflammatory cause of instability appears to be related to immunologically mediated mechanisms [62–66],which may develop in response to a variety of infectious and non-infectious stimuli.

Unusual lymphocytes that undergo clonal expansion and produce large quantities of interferon-b and pro-inflammatory cytokines in response to very restricted antigenic stimulation, which are commonly found in unstable angina, may represent mechanisms of disease similar to those postulated for rheumatoid arthritis.

The poor correlation between potential inflammatory agents and CRP levels may be at least partly explained by a variable individual response to inflammatory stimuli.

Inflammation as a trigger of instability

An inflammatory trigger of instability fits with some clinical and coronary histopathological features that are prevalent in ACS. It also provides plausible pathogenetic mechanisms of acute thrombosis and vasoconstriction, both of which are also individually modulated.

Waxing, waning and persisting inflammatory stimuli would fit nicely with the clinical pattern of waxing,

waning and recurrent instability lasting some weeks that is common in ACS. Recurring thrombotic stimuli also fit with the common autopsy finding of thrombi formed by separate layers of different age and composed of platelets[67], which suggests that such thrombi develop as a result of repeated, separate, weak thrombogenic stimuli persisting long enough to allow the progressive accumulation of platelets, but not strong enough to produce an occlusive red thrombus.

Coronary thrombosis &vasoconstriction

Activation of the vascular wall by pro-inflammatory cytokines causes the endothelium to change its properties from vasodilator and antithrombotic to constrictor and prothrombotic,to express adhesive receptors for circulating leucocytes and for platelets, and to express tissue factor.Such changes, which may be amplified by elevated CRP[68],appear by themselves sufficient to cause the formation of a local platelet-rich thrombus.

Metalloproteases, produced by activated macrophages, can cause endothelial erosion and rupture of fibrous plaques that, when highly thrombogenic,may provide a stronger stimulus capable of causing rapidly an occlusive red thrombus. For patients without signs of inflammation, typically those with infarction not preceded by unstable angina, the sudden coronary occlusion may be caused by a mechanical rather than inflammatory plaque rupture, by an irreversible coronary spasm, or by a local inflammatory process that is not detectable systemically.

However, thrombus growth is determined by individual haemostatic and vasoconstrictor responses.

Conclusion

We need to ascertain whether the inflammatory process detected systemically by elevated CRP originates in the coronary arteries or somewhere else in the body; what causes the primary or secondary inflammatory involvement of the coronary arteries; and whether the coronary vulnerable plaques are few or many.

Any single, common, putative trigger cannot explain such rarity. Thus, ACS are either the result of a very exceptional local event or of a very unusual coincidence of multiple, adverse, local and possibly systemic events that may not have the same prevalence in different ethnic, geographical, age and sex groups.

References

1) Jordan JE, Zhao ZQ, vinten-Johansen J. The role of neutrophils in myocardial ischaemia reperfusion injury. Cardiovasc Res 1999;43: 860–78.

2) Virchow R. Collected Essays on Scientific Medicine [in German].Frankfurt, Meidinger 1856.

3) Ross R. Mechanism of disease: atherosclerosis – an inflammatory disease. N Engl J Med 1999; 340: 115–26.

4) Maseri A. C-reactive protein in cardiovascular risk prediction. Zooming in and zooming out. Ital Heart J 2001; 2: 155–6.

5) Maseri A. From syndromes to specific disease mechanisms. The search for the causes of myocardial infarction. Ital Heart J 2000;1: 253–7

6) Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction. Value of combinedthrombolytic and vasodilator therapy. N Engl J Med 1987; 317:1055–9.

7) Bogaty P, Hackett D, Davies G, Maseri A. Vasoreactivity of the culprit lesion in unstable angina. Circulation 1994; 90: 5–11.

8) Pristipino C, Beltrame JF, Finocchiaro ML et al. Major racial differences in coronary constrictor response between Japanese and caucasians with recent. Circulation 2000; 101: 1102–8.

9) Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994; 331: 222–7.

10) Cannon CP,Weintraub WS, Demopoulos LA et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001; 344:1879–87.

11) Schwartz GG, Olsson AG, Ezekowitz MD et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. JAMA 2001; 285: 1711–8.

12) Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in 'active' coronary artery disease. Am J Cardiol 1990; 65: 168–72.

13) Liuzzo G, Biasucci LM, Gallimore JR et al. Prognostic value of C-reactive protein and plasma amyloid A protein in severe unstable angina. N Engl J Med 1994; 331: 417–24.

14) Toss H, Lindahl B, Siegbahn A,Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. Circulation 1997; 96: 4204–10.

15) Rebuzzi AG, Quaranta G, Liuzzo G et al. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. Am J Cardiol

1998; 82: 715–9.

16) Biasucci LM, Liuzzo G, Grillo RL et al. Elevated levels of Creactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation 1999; 99: 855–60.

17) Morrow DA, Rifai N, Antman et al. Serum amyloid A predicts early mortality in acute coronary syndromes: A TIMI 11A substudy. J Am Coll Cardiol 2000; 35: 358–62.

18) Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators.Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory to standard treatment trial. J Am Coll Cardiol 2000;35: 1535–42.

19) Biasucci LM, Liuzzo G, Colizzi C, Rizzello V. Clinical use of Creactive protein for the prognostic stratification of patients withischaemic heart disease. Ital Heart J 2001; 2: 164–71.

20) Ridker PM, Cushman M, Stamper MJ et al. Inflammation,aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973–9.

21) Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836–43.

22) Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Longterm effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE)Investigators. Circulation 1999; 100: 230–5.

23) Calabro P, Willerson JT, Yeh ETH. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation 2003;108:1930–1932.

24) Pasceri V, Willerson JT, et al. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000;102:2165–2168.

25) Pasceri V, Chang J, Willerson JT, et al. Modulation of C-reactive protein mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103:2531–2534.

26) Venugopal SK, Devaraj S, Yuhanna I, et al. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. Circulation 2002;106:1439–1441.

27) Zwaka TP, Hombach V, Torzew J. C-reactive protein-mediated low density lipoprotein uptake macrophages: Implication for atherosclerosis. Circulation 2001;103:1194–1197.

28) Yeh ET, Anderson HV, Pasceri V, et al. C-reactive protein: Linking inflammation to cardiovascular complications. Circulation 2001;104:974–975.

29) Nakogomi A, Freedman SB, Geczy CL. Interferon-gamma and lipopolysaccharide potentiate monocyte tissue factor induction by C-reactive protein: Relationship with age, sex and hormone replacement treatment. Circulation 2000;101:1785–1791.

30) Burke AP, Tracy RP, Kolodgie F, et al. Elevated C-reactive protein and atherosclerosis in sudden coronary death: Association with different pathologies. Circulation 2002;105:2019–2023.

31) Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global clinical risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813–1818.

32) Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282:2131–2135.

33) Jager A, van Hinsbergh VW, Kostense PJ, et al. Von Willebrand factor, C-reactive protein and 5-year mortality in diabetic and nondiabetic subjects: The Hoorn Study. Atheroscler Thromb Vasc Biol 1999;19:3071–3078.

34) Festa A, D'Agostino R Jr., Howard G, et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–47.

35) Ridker PM, Buring JE, Cook N, Rifai. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow up of 14,719 initially healthy American women. Circulation 2003;107:391–397.

36) Frohlich M, Imhof A, Berg G, et al. Association between C-reactive protein and features of the metabolic syndrome: A population based study. Diabetes Care 2000;23:1835–1839.

37) Ridker PM, Hennekens CH, Rifai N, et al. Hormone replacement therapy and increased plasma concentration of C-reactive protein. Circulation 1999;100:713–716.

38) Shilpak MG, Fried LF, Crump C, et al. Elevation of inflammatory and procoagulant biomarkers in elderly patients with renal insufficiency. Circulation 2003;107:32–37.

39) Liuzzo G, Biasucci LM, Rebuzzi AG et al. Plasma protein acutephase response in unstable angina is not induced by ischaemic injury. Circulation 1996; 94: 2373–80.

40) Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–1772.

41) Biasucci LM, Liuzzo G, Fantuzzi G, et al. Increased levels of interleukin (IL)-1 Ra and IL-6 during the first two days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. Circulation 1999;99:2079–2084.

42) Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin-6 and mortality in patients with unstable coronary artery disease: Effects of an early invasive or noninvasive strategy. JAMA 2001;286:2107–2113.

43) Ridker PM, Rifai N, Pfeffer M, et al., for the Cholesterol and Recurrent Events (CARE) Investigators. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation 2000;101:2149–2153.

44) Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 2000;343:1148–1155.

45) Blake GJ, Dada N, Fox JC, et al. A prospective evaluation of lipoprotein-associated phospholipase A2 levels and the risk of future cardiovascular events in women. J Am Coll Cardiol 2001;38:1302–1306.

46) Ballantyne C, et al. Lipoprotein-associated phospholipase A2 and risk for incident coronary heart disease in middle-aged men and women in the ARIC study. Presented at the American College of Cardiology, April 2, 2003

47) Kai H, Ikeda H, Yasukawa H, et al. Peripheral blood levels of MMP-2 and MMP-9 are elevated in patients with acute myocardial syndrome. J Am Coll Cardiol 1998;32:368–372.

48) Inokubo Y, Hanada H, Ishizaka H, et al. Plasma levels of MMP-9 and TIMP-1 are increased in the coronary circulation in patients with acute coronary syndrome. Am Heart J 2001;141:211–217.

49) Hirohata S, Kusachi S, Murakami M, et al. Time dependent alterations of serum MMP-1 and MMP-1 tissue inhibitor after successful reperfusion of acute coronary syndromes. Heart 1997;78:278–284.

50) Hojo Y, Ikeda U, Ueno S, et al. Expression of MMPases in patients with AMI. Jpn Circ J 2001;65:71–75.

51) Brown DL, Hibbs MS, Kearney M, et al. Identification of 92kD gelatinase in human coronary atherosclerotic lesions. Associations of active enzyme synthesis with unstable angina. Circulation 1995;91:2125–2131.

52) Ridker PM, Hennekens CH, Roitman-Johnson B, et al. Plasma concentration of soluble intercellular adhesion molecule-1 and risk of future myocardial infarction in apparently healthy men. Lancet 1998;351:88–92.

53) Liuzzo G, Biasucci LM, Gallimore JR et al. Enhanced inflammatory response in patients with pre-infarction unstable angina.J Am Coll Cardiol 1999; 34: 1696–703.

54) Bogaty P, Brecker SJ, White SE et al. Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease. Circulation 1993; 87: 1938–46.

55) Cianflone D, Ciccirillo F, Buffon A et al. Comparison of coronary angiographic narrowing in stable angina pectoris, unstable angina pectoris, and in acute myocardial infarction. Am J Cardiol 1995;76: 215–9.

56) Kol A, Sperti G, Shani J et al. Cytomegalovirus replication is not a cause of instability in unstable angina. Circulation 1995; 91:1910–3.

57) Pasceri V, Cammarota G, Patti G et al. Association of virulent Helicobacter pylori strains with ischemic heart disease. Circulation 1998; 97: 1675–9.

58) Ridker PM, Kundsin RB, Stampfer Mj et al. Prospective study of Chlamydia pneumoniae IgG seropositivity and risks of future myocardial infarction. Circulation 1999; 99: 1161–4.

59) Koening W, Rothenbacher D, Hoffmeister A et al. Infection with Helicobacter pylori is not a major independent risk factor for stable coronary heart disease. Lack of a role of cytotoxinassociated protein A-positive strains and absence of systemic inflammatory response. Circulation 1999; 100: 236–31.

60) Al-Obaidi MK, Philippou H, Stubbs PJ, Adami A, Amersey R, Noble MM, Lane DA. Relationships between homocysteine, factor VIIa and thrombin generation in acute coronary syndromes. Circulation 2000; 101: 372–7.

61) Hoffmeister A, Rothenbacher D,Wanner P et al. Seropositivity to chlamydial lipopolysaccharide and Chlamydia pneumoniae,systemic inflammation and stable coronary artery disease.Negative results of a case–control study. J Am Coll Cardiol 2000;35: 112–8.

62) Neri Serneri GG, Prisco D, Martini F et al. Acute T-cell activation is detectable in unstable angina. Circulation 1997; 95: 1806–12.

63) Aukrust P, Muller F, Ueland T et al. Enhanced levels of soluble and membrane-bound CD40 ligand in patients with unstable angina. Possible reflection of Tolymphocyte and platelet involvement in the pathogenesis of acute coronary

syndromes.Circulation 1999; 100: 614–20.

64) Liuzzo G, Kopecky SL, Frye RL et al. Perturbation of the T-cell repertoire in patients with unstable angina. Circulation 1999 100:2135–9.

65) Liuzzo G, Goronzy JJ, Yang H, Kopecky SL, Holmes DR, Frye RL, Weyand CM. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. Circulation 2000; 101: 2883–8.

66) Caligiuri G, Paulsson G, Nicoletti A, Maseri A, Hansson GK. Evidence for antigen-driven T-cell response in unstable angina. Circulation 2000; 102: 1114–9.

67) Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolisation culminating in total vascular occlusion. Circulation 1985; 71:699–708.

68) Pepys MB, Hirschfield GM. C-reactive protein and atherothrombosis. Ital Heart J 2001; 2: 196–9.

IMMEDIATE "GIK" MAY PREVENT DEATH

In a study presented at the American College of Cardiology's 61st Annual Scientific Session, Dr. Harry P. Selker and his co-investigators, claim that immediate administration of glucose mixed with insulin and potassium ("GIK") in acute coronary syndrome reduces the mortality by 50%. This is based on the assumption that the glucose provides the much needed energy to the ischaemic heart, the insulin helps to transport the glucose into the cells and the potassium corrects the hypokalaemia induced by insulin administration. Besides, the therapy is quite cheap and can be administered by trained paramedics. Whether GIK will be useful or not in a particular case is decided by using predictions of ECG based ACI-TIPI (Acute Cardiac Ischaemia - Time Insentive Predictive Instruments). The beneficial effect of this treatment is not only immediate but persists much longer to reduce the future occurrences of cardiac arrest and heart failure.

- Dr. K. Ramesh Rao

Shore Temple - Mahabalipuram

Review Article

Relationship Between Osteoporosis and Periodontitis

Dr.V. Shivakumar,* Dr.G. Sudhir, ** Dr.S. Pavithra Priyadarshini,*** Dr.M. Shanmugam,****

Chettinad Health City Medical Journal 2012; 1(1): 19 - 27

Dr.V.Shivakumar M.D.S., is working as HOD & Professor in the Department of Periodontology in Chettinad Dental College & Research Institute for past 3 years. He graduated from Government Dental College, Chennai and did his Masters in Periodontics, Annamalai University, Chidambaram. He has publication in national and international journals. He has participated and delivered guest lectures in over national and international conferences. He actively participates in community health services and research oriented programmes.

* Professor & HOD, ****Reader, Chettinad Dental College & Research Institute, Kelambakkam, Chennai.
**Registrar, Ganga Medical Centre & Hospital, Coimbatore. ***Dental Surgeon, Coimbatore.

Abstract

Periodontitis is a complex disease which may be accelerated or dampened by the innate differences among individuals and changes in environmental factors. The diagnosis is based on clinical signs and symptoms, as well as medical and dental history, the importance of determination and integration of subject-level factors, microbial composition, systemic immune response, and gingival tissue inflammatory mediator responses is being increasingly discussed. From being considered as a condition confined to the oral cavity, it is now known to branch out to the entire human body. Good oral health for good general health is gaining paramount importance. At this juncture, we aimed to bring to light the subtle connection between the two debilitating conditions osteoporosis and periodontitis through this review article. Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs. With increasing longevity of the Indian population, it is now being realized that, osteoporotic fractures are a major cause of morbidity and mortality in the elderly. Periodontitis and other periodontal inflammatory conditions are implicated in alveolar bone loss leading to tooth mobility and tooth loss. We attempt to answer the question of whether dental osteopenia is a local manifestation of osteoporosis having similar etiology and risk factors, or it is an independent process depending primarily on factors that cause periodontal disease.

Key-words: Osteoporosis, Periodontitis, Tooth mobility, Oral health, Risk factor.

Introduction

Osteoporosis is characterized by decreased bone mass and increased fracture susceptibility. Osteoporosis is a disease in which the density and quality of bone are reduced, leading to weakness of the skeleton and increased risk of fracture, particularly of the spine, wrist and hip. Osteoporosis and associated fractures are an important cause of mortality and morbidity[1]. The risk of fracture increases with age, especially in women above fifty years of age (Figure 1).

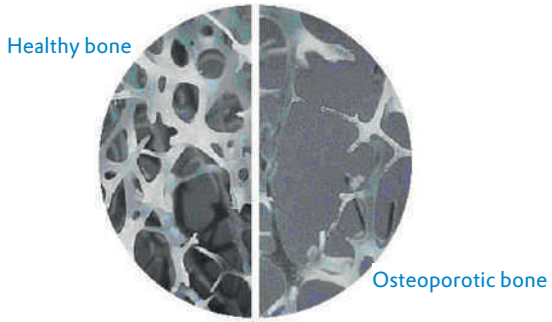


Fig.1 Healthy vs osteoporotic bone

Emotional morbidity in the form of depression, reluctance, may accompany osteoporosis. 1 out of 8 males and 1 out of 3 females in India suffers from osteoporosis, making India one of the largest affected countries in the world. In most Western countries, the peak incidence of osteoporosis occurs at about 70-80 years of age, in India it may afflict those 10-20 years younger, at age 50-60[2].

Osteoporosis can be classified as osteoclast mediated or type I and osteoblast mediated or type II. The type I is characterized by a rapid phase of bone loss predominantly involving the trabecular pattern seen in recently postmenopausal women. Women are affected 6% more frequently than men. In type II women are twice as affected as male and are related to aging, chronic calcium deficiency, increased parathyroid hormone activity and decreased bone formation[3].Osteoporosis is often called the "silent disease" because bone loss occurs without symptoms. In many cases, the first "symptom" is a broken bone. Patients with osteoporosis may not know that they have the disease until their bones become so weak that a sudden strain, bump, or fall causes a hip fracture or a vertebra to collapse. Collapsed vertebra may initially be felt or seen in the form of severe back pain, loss of height, or spinal deformities such as kyphosis, or severely stooped posture[4] (Figure 2).

The evaluation of a patient in whom osteoporosis is suspected should include a thorough medical history, imaging and laboratory studies, and possibly bone histomorphometry. A routine X-ray can reveal osteoporosis of the bone because the bones appear much thinner and lighter than normal bones.

Dual energy X ray absorptiometry (DXA) is the best current test to measure BMD. The test is quick and painless. The risk of fractures generally is lower in people with osteopenia when compared with those with osteoporosis but, if bone loss continues, the risk for fracture increases.

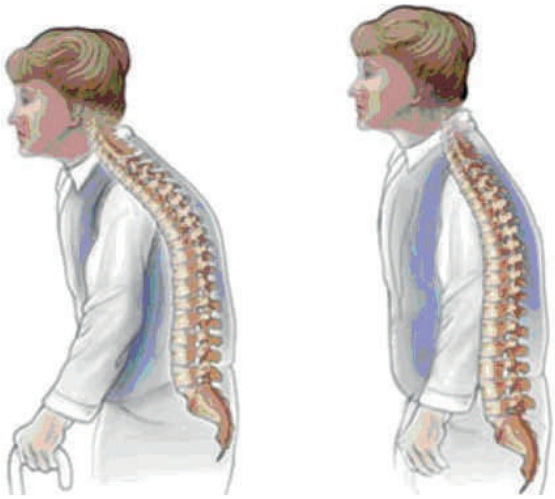


Fig.2 Age related kyphosis of spine

Risk Factors for Osteoporosis

The Non-modifiable risk factors include

- Personal history of fracture as an adult
- History of fracture in first-degree relative
- Caucasian race
- Advanced age
- Gender
- Dementia
- Poor health/frailty

The Potentially modifiable risk factors include

- Current cigarette smoking
- Low body weight (<127 lbs.)
- Estrogen deficiency
- Early menopause (<age 45) or bilateral ovariectomy
- Prolonged premenopausal amenorrhea (>1 Year)
- Low calcium intake (lifelong)
- Alcoholism
- Caffeine
- Impaired eyesight despite adequate correction
- Recurrent falls
- Inadequate physical activity

Medication

Many medications including corticosteroids, anticonvulsants, and heparin are known to decrease bone density. Prolonged corticosteroid therapy, especially in a dose of prednisone greater than 7.5 mg per day, is known to triple the risk of fracture and is the most common cause of drug-induced osteoporosis. A very recent report links accelerated bone loss to the antiretroviral class of drugs.

Drugs associated with an increased risk of generalized osteoporosis:

- Aluminum
- Anticonvulsants
- Cigarette smoking
- Cytotoxic drugs
- Excessive alcohol
- Excessive thyroxine
- Glucocorticoids and adrenocorticotropin
- Gonadotropin-releasing hormone agonists
- Heparin
- Lithium
- Tamoxifen (premenopausal use)

Bone Metabolism

Bone is a living matrix that is in a constant state of flux and under direct cellular control. Bone is formed by osteoblasts, which are cells of marrow stromal origin[5]. Bone resorption is under the control of osteoclasts. These large, multinucleated cells arise from macrophage precursors. They cause bone resorption by first isolating a segment of bone surface, thereby creating a Howships lacuna. Next, acidification solubilizes the mineral phase by means of a carbonic anhydrase mechanism, and, finally, the production of acid proteases allows for the enzymatic degradation of the organic components, including the collagen.

Frost first described the bone metabolic unit as coupled process in which resorption precedes formation[6]. Bone remodeling proceeds throughout life, and an imbalance in this process that either enhances resorption or impairs formation ultimately leads to a net loss of bone mass.

The greater the peak bone mass achieved, the better the chance of avoiding osteoporosis later in life. After peak bone mass is reached, bone loss normally occurs at the rate of 0.3 percent per year in men and 0.5 percent per year in women. A rate of bone loss of 2 to 3 per cent per year (an 8 percent decrease in trabecular bone and a 0.5 per cent decrease in cortical bone) begins at the onset of menopause. This rate continues for a period of six to ten years and then declines to a rate of 0.5 percent per year. While all adults lose bone with age, osteoporosis develops in only 20 to 30 per cent of women and 10 to 20 per cent of men who are more than sixty-five years old[7]. Many hormones directly affect bone metabolism[8]. A major one is vitamin D, a steroid hormone that plays a critical role in calcium metabolism 1,25-dihydroxyvitamin D increases absorption of calcium across the gut by maturing the villus lining cells of the intestine and stimulating them to produce

calcium-binding protein. Active vitamin D augments parathyroid hormone recruitment of osteoclasts for bone resorption by acting as a maturation hormone for the macrophage stem cell.

The second prominent hormone in bone metabolism is parathyroid hormone[8]. Parathyroid hormone responds to low ionic calcium levels by stimulating the retention of calcium and excretion of phosphate by the kidneys. In addition, parathyroid hormone indirectly increases the absorption of calcium across the gut by stimulating the conversion of 25-hydroxyvitamin D to the active metabolite 1,25- dihydroxyvitamin D in the medullary portion of the kidneys. Indirectly, by means of the osteoblast (the coupling factor leading to increased osteoclast activation), parathyroid hormone leads to bone resorption. Hence, parathyroid hormone indirectly leads to the absorption of calcium across the gut, the resorption of calcium from bone, and increased retention of calcium within the kidneys[9].

Calcitonin is a calcitropic peptide produced in the parafollicular cells of the thyroid gland. Calcitonin responds to elevated serum ionic calcium levels by decreasing the number and activity of osteoclasts[10]. Calcitonin also functions as a neuropeptide and has analgesic effects. It primarily decreases bone resorption and secondarily causes a transient increase in bone formation by means of a still unknown mechanism.

A normal balance of oestrogen and progesterone is critical for the maintenance of bone mass. Young women who have episodes of amenorrhoea or oligomenorrhoea before peak bone mass is attained lose 2 per cent of bone mass per year instead of gaining 2 to 4 per cent per year as they would normally[11]. This loss is oestrogen-dependent, and the bone mass that is lost is not regained once normal menstrual cycles are resumed. The level of circulating oestrogen declines after menopause. Some women have a rapid acceleration of bone loss secondary to increased bone-remodeling, with bone resorption exceeding bone formatio[n11]2

Association of Osteoporosis and Periodontitis

Periodontitis is charecterised by inflammation and loss of connective tissue and alveolar bone. Like osteoporosis, it is a silent disease causing symptoms until late in the disease process when mobile teeth, abscesses and tooth loss may occur. Both osteoporosis and periodontal disease share many risk factors and since both are bone resorptive diseases it has been hypothesized that osteoporosis could influence progression of periodontal disease. In the last ten years a large amount of research was done on the influence of systemic bone mass loss in osteoporosis on the periodontal disease appearance. Krall et al[13] thinks that alveolar bone loss in patients with lower bone mineral density can be faster and less resistant to therapy than in patients with normal bone density. Jeffcoat came to the conclusion that a quarter of postmenopausal women have faster bone mass loss (5-8% a year) and are at higher risk for alveolar bone loss and periodontal disease[14].

Another study showed that the average values of pocket depth in healthy patients (M = 3.51) are statistically significantly lower (at 98% significance level) than the average values of pocket depth in patients with osteoporosis (M = 4.14). The presence of the combined type of bone resorption is more frequent (at 97% significance level) in patients with osteoporosis (f = 5) in comparison to healthy ones[15]. Tezal et al., Pilgrae et al. and Chohayeb connect skeleton bone mass density BMD with alveolar bone loss and also with evident clinical connection loss and they conclude that there is a connection between postmenopausal osteoporosis and periodontal status. The average pocket depth value is statistically significantly different in relation to skeleton BMD[16, 17, 18].

The results arrived in a study by Hildebolt, Shen et al. and Von Wowen et al. were that BMD does change with age and that the change is accompanied by alveolar bone changes[19,20,21]. Geurs et al. studied the connection between systemic bone loss (measured by DXA) and periodontal disease (measured by periodontal pocket depth). They concluded that the patients with osteoporosis have greater epithelial connective tissue loss than the patients without osteoporosis, i.e. that the greatest epithelial connective tissue loss is in patients with both periodontal disease and osteoporosis. Geurs et al. considered osteoporosis or lower values of skeleton BMD should be considered as a risk factor for the development of periodontal disease[22]. In their study, Wactawski-Wende,[23] discovered a significant connection between periodontal connective tissue loss, as an indicator for periodontitis, and skeleton osteoporosis measured by DXA, especially in postmenopausal women. Klemetti et al. studied the postmenopausal women with significantly deep priodontal pockets and detected greater BMD loss in relation to the patients with shallow periodontal pocket or no periodontal pockets. On the basis of their research they concluded that there is a relation between BMD and periodontal disease[24]. A study has shown that after fifty years of age the porosity of the mandibular cortical bone increases markedly especially in the alveolar bone, at the same time there is a decrease in bone mass[25]. These changes are greater in women than in men and this is reflected in the fact that women have a lower mandibular BMD than men. This sex difference in BMD value is also observed in other bones. It has been suggested that this increase in alveolar bone porosity in combination with local factors could be of etiological importance in the rate of periodontal alveolar bone loss which leads to periodontal disease. Some authors have experimentally concluded that in postmenopausal women BMD is related to interproximal alveolar bone loss. This conclusion points at postmenopausal osteopenia as a possible risk factor for periodontal disease in postmenopausal women[26].

Another study has shown that women with high calculus apposition and low BMD had greater clinical gingival attachment loss than women with normal BMD and similar calculus apposition[27]. Still other authors have reported that serum oestradiol supplementation, in early menopausal osteoporotic women, reduces gingival inflammation and attachment loss[28].

A study performed on digitized periapical radiographs of the maxilla and mandible obtained from osteoporotic patients and normal controls lends support to the hypothesis that osteoporotic patients present an altered trabecular pattern in the jaw bones when compared to normal controls[29].

Radiographic evaluation of alveolar bone loss was conducted in a 2-year longitudinal clinical study on 21 women with normal BMD of the lumbar spine, and 17 women with osteoporosis or osteopenia of the lumbar spine at baseline. These 38 patients had a history of periodontitis and were non-smokers. The results of this study showed that osteoporotic/osteopenic women exhibited a higher frequency of alveolar bone height loss ($p<0.05$) and crestal ($p<0.025$) and subcrestal ($p<0.03$) density loss relative to women with normal BMD. Additionally it was shown that oestrogen deficiency in the osteoporotic/osteopenic women was associated with increased alveolar bone crestal density loss. This study data suggests that oestrogen deficiency and osteoporosis/osteopenia could be considered potential risk factors for alveolar bone loss in postmenopausal women with periodontitis[30].

Pilgram et al have concluded that there is no definite association between clinical attachment level and BMD of the lumbar spine and the femur. They also conclude that there may be a weak association between BMD and longitudinal changes in attachment level[31]. Histomorphometric and micro radiographic studies showed that people aged more than 50 years experience significant changes in the osseous tissue, occurring in mandibular trabecular and cortical bone tissue, and increasing porosity of the cortical layer results in the decrease in bone mass[32]. E Manzke et al[33] raised a hypothesis that systemic imbalance in bone resorption and deposition may manifest itself in the alveolar bone earlier than in other bones. During a long period of the research, a number of comparative studies on different bones (e.g. spinal vertebrae and mandible, mandible and radius, wrist, thigh-bone, and other bones of the skeleton) were performed[34], and it was suggested to pay attention to the influence of systemic factors that are responsible for the development of the osteoporotic process and to the relationship of these factors with the local ones that increase the alveolar resorption of mandible. Due to its anatomical–morphological properties, maxilla was rarely used in the studies of changes in osseous tissues.

J. J. Groen et al[35] thought that spinal vertebrae and the mandible had similar muscle fixation, and therefore, they compared radiograms and raised a hypothesis that radiograms of alveolar processes could be good indicators for the diagnosis of systemic osteoporosis . These authors have even proposed a term – "alveolar or periodontal osteoporosis". P. J. Kribbs in 1983[36] and 1989[37]and N. Von Wowern[38] in 1994 concluded that mandibular osseous mass correlated with the total skeletal bone mass. The majority of performed studies showed that a relationship existed between total skeletal bone mass and the amount of oestrogens in the organism, and that diminution of oestrogen levels affected the bone density of the jaws.

A. R. Becker[39] who performed his investigation in 1997, determined a negative correlation between the number of remaining teeth and the time of the beginning of menopause in women of postmenopausal age in whom no hormone replacement therapy was applied. R. E. Persson in 1998[40] and J. B. Payne in 1999[41] studied older women who underwent hormone replacement therapy and concluded that periodontium in such women was healthier than in those who did not receive such treatment. A.Taguchi in 1995[42] and L. Birkenfeld in 1999[43] performed a descriptive study on women who had experienced spinal fractures. The majority of them had periodontitis and few remaining teeth in the oral cavity. The authors suggested that there could be a high percentage of people with periodontal diseases among those with osteoporosis. Not all studies confirmed the presence of a relationship between periodontal diseases and osteoporosis, In a study of 70 year old women 15 subjects with osteoporosis were compared to 21 subjects with normal BMD. No statistically significant difference was found in gingival bleeding, probing pocket depths, gingival recession or marginal bone level between the women with osteoporosis and the women with normal BMD[44].

In a report by Elders et al.,[45]lumbar BMD and metacarpal cortical thickness were compared to alveolar bone height on bitewing radiographs and clinical parameters of periodontitis. No significant relation was found between bone mass measurements and alveolar bone height and periodontal parameters. The mean age of this study was[46]- 55 yrs, consisting of younger population, and could have contributed to the lack of correlation. In August 1992, a relationship between oral and skeletal osteoporosis was confirmed, and an agreement on the necessity of radiological diagnosis was made 44. In 1992, the US National Health Institute ordered special studies for the determination of the relationship between oral condition and osteoporosis. The application of the panoramic radiogram test for people with osteoporosis for the confirmation of the diagnosis of periodontitis was among the set objectives. M. G. Perno in 2002 stated that it was well known how to treat osteoporosis or periodontal diseases separately, but there was no clear definition concerning how to treat patients who have both diseases . The question of whether curative means and measures applied for osteoporosis are also effective in periodontitis still remains unanswered46.

M. Tezal et al[47]states that changes in the systemic bone density also simultaneously entail changes in the height and the density of the alveolar bone and changes in the height of the clinical junction of periodontal tissues . F. Grodstein[48] in his studies found that women who had osteoporosis and underwent oestrogen therapy had a significantly higher probability to preserve their teeth, whereas women with osteoporosis who did not undergo any oestrogen therapy and poorly performed oral hygiene procedures had a high risk of losing their teeth. This risk may be reduced by prescribing treatment with hormone preparations.

A cross-sectional study in a group of[50] normal women aged 20-90 years was done and it was inferred that the mandibular bone mass correlated with the bone mass

at spine and wrist. In another study a comparison of 85 osteoporotic women and 27 normal women were compared. The osteoporotic group had less mandibular bone mass and density and a thinner cortex at the gonion than the normal group. In another study done by the same author on 85 osteoporotic post-menopausal women the total body calcium, bone mass at radius and bone density at the spine correlated with mandibular mass.

Prevention and Treatment

The goal of treatment of osteoporosis is the prevention of bone fractures by reducing bone loss or, preferably, by increasing bone density and strength. Although early detection and timely treatment of osteoporosis can substantially decrease the risk of future fractures, none of the available treatments for osteoporosis are complete cures. The following are osteoporosis treatment and prevention measures. Calcium is one of the most widely used agents in the treatment of osteoporosis[49]. Calcium supplementation in the older population may be most effective when the baseline calcium intake is less than 400 milligrams per day, for those who have an intestinal malabsorption syndrome, or in combination with an exercise regimen[50]. Calcium supplementation is helpful for patients who have type-II osteoporosis, especially when the therapy is combined with vitamin-D supplementation[51]. A marked decrease in the rate of fractures of the hip was demonstrated in a study of elderly patients from France who had received dietary supplements of calcium and vitamin-D. This decrease occurred even though little difference was noted in bone mass, a finding that raises the possibility that the calcium and vitamin-D supplementation had improved the quality of bone or had decreased the prevalence of secondary hyperparathyroidism[52].

Vitamin-D stimulates bone formation and intestinal calcium absorption; vitamin-D supplementation therefore may improve calcium balance. In addition, vitamin-D may positively influence bone density in healthy individuals who do not have vitamin-D deficiency or osteoporosis by suppressing parathyroid hormone activity[53]. Several recent studies have shown that the oral administration of calcitriol and some of its synthetic precursors, notably alfa calcidol (1-alpha-hydroxyvitamin D3), can correct mild secondary hyper parathyroidism, reduce bone loss, and prevent fractures of the hip[54, 55]

Oestrogen deficiency plays a prominent role in the pathogenesis of osteoporosis. Estrogen inhibits bone resorption and positively affects calcium balance, either directly, by stimulating the estrogen receptors in bone, or indirectly, by suppressing the production of bone-resorbing cytokines; inhibits osteoclast formation and function and can also extend the lifespan of osteoblasts and osteocytes[56, 57]. The administration of estrogen to postmenopausal women not only prevents bone loss but also protects against vertebral and femoral fractures, with a greater effect on the spine [58]. Discontinuation of the therapy is followed by an immediate resumption of bone loss at a rate similar to that in women who have not received such therapy[59].

Dose of estrogen required to prevent bone loss is 0.625 milligram, but half of this dose may suffice when it is combined with calcium supplementation[60]. Prolonged use of estrogen appears to increase the risk of breast cancer by 30 per cent[61, 62], an increase roughly from eleven to fourteen instances of breast cancer per 100 women. The concomitant administration of progestin eliminates the risk of uterine cancer, and continuous therapy with a combination of progestin and estrogen can minimize cyclical uterine bleeding in older women 60. Most of the cardiovascular benefits associated with estrogen are preserved when progestin is given cyclically, but the continuous use of progestin diminishes some of the cardiovascular benefits of estrogen. Selective estrogen receptor modulators provide benefits of estrogen without its unwanted side effects. The mechanism of action such as that of raloxifene is similar to that of the estrogens. Reduction of fracture was seen in first year of treatment but no effect was found on the risk of non-vertebral fractures [63]. Similar to estrogen therapy, an increase in the incidence of deep vein thrombosis was observed. New selective estrogen receptor modulators are researched and may be available in the near future.

Calcitonin typically is administered by means of subcutaneous injection and also has been shown to be effective in intranasal, rectal, and transdermal forms, although there may be erratic patterns of absorption with the nasal route. The analgesic effects of the newly released nasal form are similar to those of the other forms. Reginster et al.[64] conducted a three-year randomized placebo-controlled study in which women in whom menopause had taken place six to thirty-six months previously were given either calcium alone or the same amount of calcium in addition to calcitonin by means of nasal administration.

Bisphosphonates are stable, active analogs of pyrophosphate that both inhibit osteoclastic resorption and depress bone turnover[65]. Etidronate and newer bisphosphonates, including alendronate, pamidronate, residronate, taludrinate, and clonodrate, currently are the most extensively investigated agents in osteoporosis research[66]. Etidronate is most effective during the first two years of therapy[67]. Bisphosphonates appear to be effective in the five-year period of rapid bone turnover that occurs after menopause. Bisphosphonates primarily act on trabecular bone and are less effective in preventing the loss of compact bone as well as fractures of the hip[68].

The second-generation agents are more potent and yet cause less inhibition of mineralization than Etidronate [69]. Alendronate, recently approved by the Food and Drug Administration, appears to prevent vertebral bone loss in patients who have osteoporosis and does not alter the mechanical properties of bone4. In addition, it appears to continue to work even after it is no longer being administered. Rossini et al.[70] recently reported that lumbar bone-mineral density increased by 3.7 ± 1.7 per cent (average and standard deviation) after six months of Alendronate therapy and did not change six and twelve months after the cessation of treatment.

The occurrence of osteonecrosis of the jaw with the use of bisphosphonate is a concern to dental community. Osteonecrosis of the jaws occurs more commonly in the mandible but has also been reported in the maxilla, and appears to be highly associated with periodontitis, other oral infections, and extraction of the affected teeth in majority of the reported cases. In addition the signs and symptoms that may occur before the appearance of clinically evident osteonecrosis include changes in the health of the periodontal tissues, non- healing mucosal ulcers, loose teeth, unexplained soft tissue infection. The role of bisphosphonates in osteonecrosis of the jaw needs to be further evaluated.

In contrast to the antiresorptive drugs described previously, fluoride causes osteoblast proliferation and stimulates new bone formation. Researchers have found substantial increases in trabecular bone in patients who had received fluoride[71]. Enthusiasm for fluoride has been tempered by studies that have shown impaired bone mineralization and increased rates of fractures of the hip and vertebrae despite increased bone density in the lumbar spine[72]. Patients in whom osteoporosis is treated with fluoride often have a calcium deficiency because of increased mineralization of trabecular bone. This renders the patients vulnerable to secondary hyperparathyroidism. Vitamin-D supplementation can correct the calcium deficiency while potentiating the effect of fluoride on the osteoblast; this allows the dose of fluoride to be decreased and thereby minimizes its side effects 73. The ideal role of fluoride in the future may be to augment bone density at the initiation of therapy before switching to antiresorptive agents for the long-term maintenance of bone density. At the present time, however, the use of fluoride is considered experimental.

Conclusion

The current studies point at a possible correlation between osteoporotic bone loss and periodontal bone loss. Further studies are required in this direction to facilitate answers to many questions. Is dental osteopenia a local manifestation of osteoporosis having similar etiology and risk factors, or whether it is an independent process depending primarily on factors that cause periodontal disease? What research techniques are precise enough for determining bone density in the mandible? How does the osteoporotic process damage different skeletal structures? Is periodontitis the first prognostic sign of osteoporotic changes in spine and long bones? Periodontist and Orthopaedicians should understand the effects of osteoporosis on both systemic and oral health. These two health care providers working hand in hand could increase the awareness among people, offer early diagnosis of the disease, elucidate solutions and fabricate a treatment modality to bring these two debilitating conditions in check.

REFERENCE

1) International Osteoporosis Foundation (IOF) http://www.iofbonehealth.org/patients-public/about osteoporosis.html

2) Damodaran P, Subramaniam R, Omar SZ, Nadkarni P, Paramsothy M., Singapore Med J. 2000 Sep; 41(9): 431-5, "Profile of a menopause clinic in an urban population in Malaysia

3) American Academy of Orthopaedic Surgeons: A position statement: prevention of hip fractures. Rosemont, Illinois, The American Academy of Orthopaedic Surgeons, 1993

4) National Instititutes of Health Osteoporosis and Related Bone Disease-National Resource Center http://www.osteo.org 2004

5) Lane, J. M.; Cornell, C. N.; and Healey, J. H.: Orthopaedic consequences of osteoporosis. In Osteoporosis. Etiology, Diagnosis and Management, pp. 433-455. Edited by B. L. Riggs and L. J. Melton, III. New York, Raven Press, 1988.

6) Frost, H. M.: Bone Remodeling Dynamics. Springfield, Illinois, Charles C Thomas, 1963

7) Kassem, M.; Mosekilde, L.; and Eriksen, E. F.: 1,25-dihydroxyvitamin D3 potentiates fluoride-stimulated collagen type I production in cultures of human bone marrow stromal osteoblast-like cells. / Bone and Min. Res., 8:1453-1458,1993

8) Cummings, S. R.; Kelsey, J. L.; Nevitt, M. C; and O'Dowd, K. J.: Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol. Rev., 7:178-208,1985.

9) Lane, J. M., and Healey, J. H. [editors]: Diagnosis and Management of Pathological Fractures. New York, Raven Press, 1993.

10) Wong, G. L.: Skeletal effects of parathyroid hormone. In Bone and Mineral Research/4, edited by W. Peck. Ed. 4, pp. 103-130. Amsterdam, Elsevier, 1986.

11) Austin, L. A., and Heath, H., Ill: Calcitonin: physiology and pathophysiology. New England J. Med., 304: 269-278,1981.

12) Cann, C. E.; Cavanaugh, D. J.; Schnurfield, K.; and Martin, M. C: Menstrual history is the primary determinant of trabecular bone density in women runners [abstract]. Med. and Sci. Sports and Exerc, 20 (Supplementum): 559,1988.

13) Krall EA, The Oral Effects of Osteoporosis. Nutr Clin Care. 2001;4:22-7.

14) Jeffcoat M. The association between osteoporosis and oral bone loss. J Periodontol. 2005;76(11 Suppl):2125-32.

15) Bone levels in patients with osteoporosis and periodontal disease Mirjana Gojkov-Vukelić1, Mirjana Malić1, Sanja Hadžić1, Lidija Lincender2 Acta Medica Academica 2007; 36: 76-81

16) Tezal M, Wactawski-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol. 2000;71(9):1492-8.

17) Pilgram TK, Hildebolt CF, Yokoyama-Crothers N, Dotson M, Cohen SC, Hauser JF et al. Relationship between longitudinal changes in radiographic alveolar bone height and probing depth measurement: Data from postmenopausal women. J Periodontol. 1999;70:829-33.

18) Chohayeb AA. Influence of osteoporosis on the oral health of menopausal women. General Dentistry. 2003;258-.

19) Hildebolt CF, Pilgram TK, Yokoyama-Crothers N, Vannier MW, Dotson M, Muckerman J, et al. Alveolar bone height and postcranial bone mineral density: Negative effects of cigarette smoking and parity. J Periodontal. 2000;71: 683-9.

20) Shen EC, Gau CH, Hsieh Yd, Chang CY, Fu E. Periodontal status in post menopausal osteoporosis : a preliminary clinical study in Taiwanese women. J Chin Med Assoc. 2004;67:389-93.

21) Von Wowern N. General and oral aspects of osteoporosis: a review. Clin Oral Invest. 2001;5:71-82.

22) Geurs NC, Lewis CE, Jeffcoat MK. Osteoporosis and periodontal disease progression. Periodontology.2000;32:105-10.

23) Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol. 2001;6:197-208.

24) Klemetti E, Collin HL, Forss H, Markkanen H&Lassila V. Mineral status of skeleton and advanced periodontal disease. J Clin Periodontol. 1994;21:184-8.

25) Hildebolt,CF.Osteoporosis and oral bone loss.Dento-Maxillo-fac Radiol 1997;26:3-15.

26) Tezal, M et al. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2000;71:1492-8.

27) Ronderos, M et al. Associations of periodontal disease with femoral bone mineral density and estrogen replacement therapy: cross-sectional evaluation of US adults from NHANES III. J Clin Periodontol 2000;27:778-86.

28) Reinhardt, RA et al. Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. J Periodontol 1999;70:823-8.

29) White, SC; Rudolph, DJ. Alterations of the trabecular pattern of the jaws in patients with osteoporosis. Oral Sur Oral Med Oral Pathol Oral Radiol Endod 1999;88:628-35.

30) Payne, JB; Reinhardt, RA; Nummikoski, PV; Patil, KD.Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. Osteoporosis International 1999;10:34-40.

31) Pilgram TK et al. Relationships between clinical attachment level and spine and hip bone mineral density: data from healthy postmenopausal women. J Periodontol 2002;73:298-301.

32) Hildebolt CF. Osteoporosis and oral bone loss. Dentomaxillofac Radiol 1997;26:3-15.

33) Manzke E, Chesnut CH III, Wergedal JE, Baylink DJ, Nelp WB. Relationship between local and total bone mass in osteoporosis. Metabolism 1975;24:605-15.

34) Haimov-Kochman R, Kochman T, Stabholz A, Hochner- Celinkier D. Bisphosphonate and estrogen replacement therapy for postmenopausal periodontitis. IMAJ 2004;6:173-6.

35) Groen JJ, Duyvensz F, Halsted JA. Diffuse alveolar atrophy of the jaw (non-inflammatory form of paradental disease) and presenile osteoporosis. Geront Clin 1960;2:68-86.

36) Kribbs PJ, Smith DE, Chesnut CH 3rd. Oral findings in osteoporosis. Part I. Measurement of mandibular bone density. J Prosthetic Dentistry 1983;50(4):576-9

37) Kribbs PJ, Chesnut C, Ott SM, et al. Relationships between mandibular and skeletal bone in an osteoporotic population. J Prosthetic Dentistry 1989;62:703-6.

38) von Wowern N, Klausen B, Kollerup G. Osteoporosis: a risk factor in periodontal disease. J Periodontol 1994;65(12):1134-8.

39) Becker AR, Handick KE, Roberts WE, Garetto LP. Osteoporosis risk factors in female dental patients. A preliminary report. J Indiana Dental Assoc 1997;76:15-9.

40) Persson RE, Persson GR, Kiyak HA, Powel LV. Oral health and medical status in dentate low-income older persons. Spec Care Dentist 1998;18:70-7.

41) Payne JB, Reinhardt RA, Nummikoski PV, Patil KD. Longitudinal alveolar bone loss in postmenopausal osteoporotic/ osteopenic women. Osteoporosis Int 1999;10:34-40.

42) Taguchi A, Tanimoto K, Suei Y, Otani K, Wada T. Oral signs as indicators of possible osteoporosis in elderly women. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:612-6.

43) Birkenfeld L, Yemini M, Kase NG, Birkenfeld A. Menopauserelated alveolar bone resorption: a review of relatively unexplored consequences of estrogen deficiency. Menopause 1999; 6:129-33.

44) Hildebolt CF. Osteoporosis and oral bone loss. Dentomaxillofac Radiol 1997;26:3-15

45) Elders PJ,Habetts LL,Netelenbos JC, Linden LW,Stelt PF The relationship between periodontitis and systemic bone loss in women between 46 and 55 years of age J Clinical Periodontol1992:19 492-6

46) Goldi MP. Osteoporosis. Periotrends 2002;7:34-7.

47) Tezal M, Wactawsky-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2000;71:1492-98.

48) Grodstein F, Colditz GA, Stampfer MJ. Post-menopausal hormone use and tooth loss: a prospective study. J Am Dent Assoc 1996;127:370-7.

49) Heaney, R.P.: Calcium in the prevention and treatment of osteoporosis. J.Intern.Med., 231:169-180,1992

50) Dawson-Hughes, B.; Dallal, G. E.; Krall, E. A.; Sadowski, L.; Sahyoun, N.; and Tannenbaum, S.: A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. New England J. Med., 323: 878-883,1990.

51) Buckwalter, J. A.; Glimcher, M. J.; Cooper, R. R.; and Recker, R.: Bone biology. Part II: formation, form, modeling, remodeling, and regulation of cell function. J. Bone and Joint Surg., 77-A: 1276-1289, Aug. 1995.

52) Chapuy, M. C; Arlot, M. E.; Duboeuf, F.; Brun, J.; Crouzet, B.; Arnaud, S.; Delmas, P. D.; and Meunier, P. J.: Vitamin D3 and calcium to prevent hip fractures in the elderly women. New England J. Med., 327:1637-1642,1992

53) Khaw, K. T.; Scragg, R.; and Murphy, S.: Single-dose cholecalciferol suppresses the winter increase in parathyroid hormone concentrations in healthy older men and women: a randomized trial. Am. J. Clin. Nutr., 59:1040-1044,1994

54) Orimo, H.; Shiraki, M.; Hayashi, T.; and Nakamura, T.: Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. Bone and Min., 3: 47-52,1987.

55) Menczel, J.; Foldes, J.; Steinberg, R.; Leichter, I.; Shalita, B.; Bdolah-Abram, T.; Kadosh, S.; Mazor, Z.; and Ladkani, D.: Alfacalcidol (alpha D3) and calcium in osteoporosis. Clin. Or/hop., 300: 241-247,1994.

56) Hui, S. L.; Slemenda, C. W.; and Johnston, C. C, Jr.: Baseline measurement of bone mass predicts fracture in white women. Ann. Intern.Med., 111:355-361,1989.

57) Jilka, R. L.; Hangoc, G.; Girasole, G.; Passeri, G.; Williams, D. C; Abrams, J. S.; Boyce, B.; Broxmeyer, H.; and Manolagas, S. C: Increased osteoclast development after estrogen loss: mediation by interleukin-6. Science, 257: 88-91,1992.

58) Ettinger, B.; Genant, H. K.; and Cann, C. E.: Long-term estrogen replacement therapy prevents bone loss and fractures. Ann. Intern. Med., 102:319-324,1985.

59) Buckwalter, J. A.; Glimcher, M. J.; Cooper, R. R.; and Recker, R.: Bone biology. Part II: formation, form, modeling, remodeling, and regulation of cell function. J. Bone and Joint Surg., 77-A: 1276-1289, Aug. 1995.

60) Session, D. R.; Kelly, A. C; and Jewelewicz, R.: Current concepts in estrogen replacement therapy in the menopause. Fertil. and Sterii, 59:277-284,1993.

61) Colditz, G. A.; Egan, K. M.; and Stampfer, M. J.: Hormone replacement therapy and risk of breast cancer: results of epidemiologic studies. Am../. Obstet. and Gynec, 168:1473-1480,1993.

62) Colditz, G. A.; Hankinson, S. E.; Hunter, D. J.; Willet, W. C; Manson, J. E.; Stampfer, M. J.; Hennekens, C; Rosner, B.; and Speizer, F. E.: The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. New England J. Med., 332:1589-1593,1995

63) Riggs B.L., Hartmann L.C. Selective estrogen receptor modulators: Mechanism of action and application to clinical practice New England J. Med.,2003.348;618-29

64) Reginster, J. Y.; Denis, D.; Deroisy, R.; Lecart, M. P.; De Longueville, M.; Zegels, B.; Sarlet, N.; Noirfalisse, P.; and Franchimont, P.:Long-term (3 years) prevention of trabecular postmenopausal bone loss with low-dose intermittent nasal salmon calcitonin. J. Bone ana'Min. Res., 9:69-72,1994.

65) Endo, Y.; Nakamura, M.; Kikuchi, T.; Shinoda, H.; Takeda, Y.; Nitta, Y.; and Kumagai, K.: Aminoalkybisphospbonates, potent inhibitorsof bone resorption, induce a prolonged stimulation of histamine synthesis and increase macrophages, granulocytes, and osteoclasts in vivo. Calcif. Tissue Internal, 52: 248-254,1993

66) Ott, S. M.: Clinical effect of bisphosphonates in involutional osteoporosis./ Bone and Min. Res., 8 (Supplement 2): S597-S606,1993.

67) Harris, S. T.; Watts, N. B.; Jackson, R. D.; Genant, H. K.; Wasnich, R. D.; Ross, P.; Miller, P. D.; Licata, A. A.; and Chesnut, C. H., Ill:Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am. J. Med., 95: 557-567,1993.

68) Storm, T.; Thamsborg, G.; Steiniche, T.; Genant, H. K.; and Sorensen, O. H.: Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. New England J. Med., 32:1265-1271,1990.

69) Toolan, B. C; Shea, M.; Myers, E. R.; Hayes, W. C; Thompson, D. D.; Seedor, J. G.; Quartuccio, H.; Klein, H. J.; Jackson, R.; Fioravanti, C; Gibson, R. E.; Clair, J.; and Rodan, G. A.: The effect of long term alendronate treatment on vertebral strength in ovariectomized baboons and rats [abstract]./ Bone and Min. Res., (Supplement 1): S248,1991.

70) Rossini, M.; Gatti, D.; Zamberian, N.; Braga, V.; Dorizzi, R.; and Adami, S.: Long-term effects of a treatment course with oral alendronate of postmenopausal osteoporosis. J. Bone and Min. Res, 9:1833-1837,1994.

71) Boivin, G.; Dupuis, J.; and Meunier, P. J.: Fluoride and osteoporosis. In Osteoporosis: Nutritional Aspects. World Review of Nutrition and Dietetics, edited by A. P. Simopoulos and C. Galli. Vol. 73, pp. 80-103. Basel, Switzerland, Karger, 1993.

72) Riggs, B. L.; Hodgson, S. E; O'Fallon, W. M.; Chao, E. Y.; Wahner, H. W.; Muhs, J. M.; Cadel, S. L.; and Melton, L. J., Ill: Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. New England J. Med., 322: 802-809,1990.

73) Heaney, R. P.; Recker, R. R.; and Saville, P. D.: Menopausal changes in bone remodelling. /. Lab. and Clin. Med., 92:964-970,1978.

Chettinad Hospital & Research Institute

Case Report
Seckel Syndrome

Dr. Jaishree Vasudevan,* Dr. Karthik Surya R,** Dr. Thayumanavan S***

Chettinad Health City Medical Journal 2012; 1(1): 28 - 30

Dr. Jaishree Vasudevan obtained her M.B.,B.S degree from the prestigious Devi Ahilya Vishwa Vidyalaya Indore in 1993 and her M.D degree in Paediatrics in 1996 from Pandit Ravi Shankar Shukla University , Raipur. She worked in Indraprastha Apollo hospital, Delhi following post-graduation and relocated to Chennai in 2000. She joined the present institution as Assistant Professor , Paediatrics in 2006 and is presently working as Associate Professor. Her special interests are genetics and nutrition in Paediatrics.

*Associate professor, **Senior Resident, ***Professor & HOD, Dept. of Paediatrics

Abstract

Though short stature is not uncommon in pediatric practice, there are only a few conditions where the growth retardation is very severe. One of them is Seckel syndrome, which is a cause for primordial dwarfism, and is extremely rare. The reported incidence is 1 in 10000[1] live births. We report a case of Seckel syndrome in a 14 month old child.

Key-words: Seckel Syndrome, Short stature, Dwarfism

Case report

14 months old male baby born of 3rd degree consanguinous marriage presented with dyspnea and tachypnea of 2 days duration, with past history of recurrent upper respiratory tract infection. The patient was a preterm baby with intrauterine growth retardation and was delivered at 32 weeks gestation age with a birth weight of 750 grams. He was admitted in NICU for the first 15 days of life and USG cranium showed features of hypoxic ischemic encephalopathy.

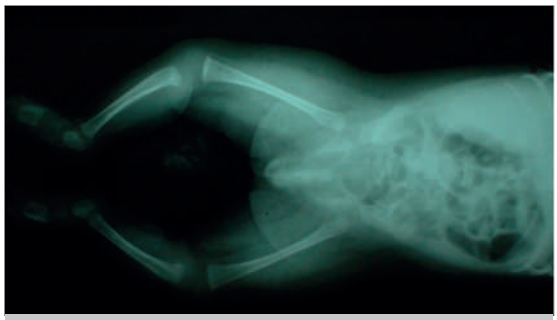


Figure 1 X ray both knees, showing delayed skeletal maturation

Figure 2 Clinical photograph

At present the child's chronological age is fourteen months. He weighs 2.4kg, length is 49.5cms and his head circumference is 34.5 cm. All these parameters fall below the 5th percentile. He has a flat occiput and sparse scalp hair. His anterior fontanelle is closed. He has an antimongoloid slant, low set small ears, prominent eyes, beaked nose, micrognathia, 5th finger clinodactyly and left undescended testis with mild hypotonia.

He has achieved head control and rolls over and creeps. He is active, babbles and recognizes immediate care givers. He is anemic with hemoglobin of 9.4gm%. He is euthyroid. X-rays of his skull and both hands showed findings of clinodactyly, delayed skeletal maturation and relative microcephaly with normal sutures. Chromosomal studies revealed a normal karyotype. These findings and his phenotype are consistent with Seckel syndrome.

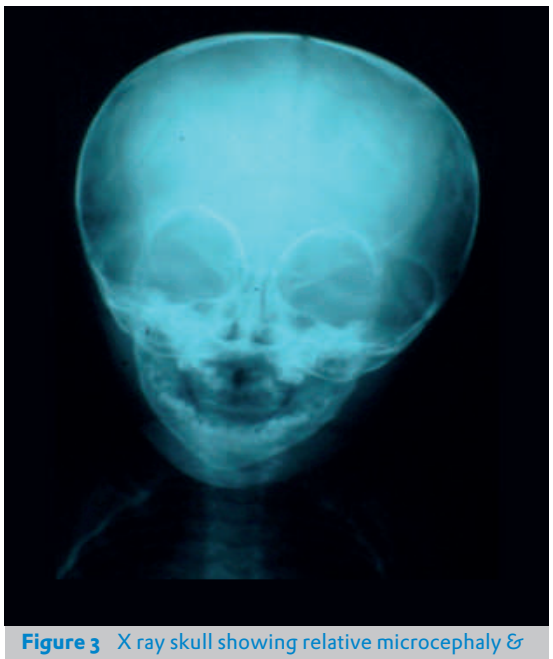


Figure 3 X ray skull showing relative microcephaly & normal sutures

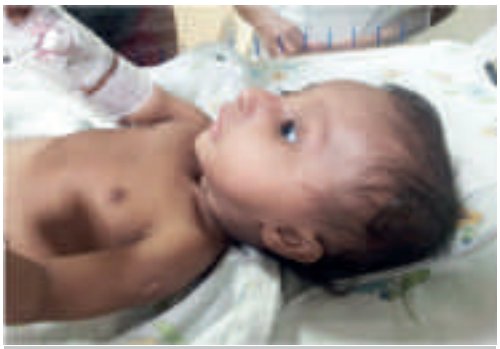


Figure 4 Clinical photograph – prominent nose, micrognathia (bird headed dwarfism)

Discussion

Seckel syndrome is a genetic disorder characterized by microcephaly and mental retardation with unique facial features with large eyes, beak like nose, narrow face and receding lower jaw[2]. Mental retardation is not as marked as might be expected in view of the very small brain[3]. The signs and symptoms of Seckel syndrome may be similar to those of another condition called microcephalic osteodysplastic primordial dwarfism type 2. Microcephalic osteodysplastic primordial dwarfism (MOPD) is characterized by intrauterine and postnatal growth retardation, short limbs (brachymelia), and microcephaly. However MOPD2 is associated with abnormalities of the bones which can be identified by performing X-rays during the first years of life. The humeri and femora are broad, shortened, and bowed in MOPD 2.

Seckel syndrome is a heterogeneous, autosomal recessive disorder that has been subclassified into types 1 through 4 depending on linkage to different chromosomal regions (3q22, 18p11, 14q, 21q22.3). The clinical characteristics of patients with Seckel syndrome type 4 (chromosome 21q22.3-qter; OMIM 611860) are similar to those of patients with other subtypes. Griffith et al[5], utilizing a genome wide association procedure in 2 consanguineous families with Seckel syndrome members, also localized the disorder to chromosome 21q22.3 and identified homozygous inactivating (nonsense, single base pair deletion or insertion) mutations in pericentrin 2 (PCNT2) in affected patients.

The centrosome is a cytoplasmic organelle that prepares the mitotic spindle for chromosome segregation and also regulates progression of the cell cycle through mitosis. Pericentrin 2 (PCNT2) is a centrosomal protein that is essential for the integrity of the mitotic spindle as it links the microtubules of the mitotic spindle apparatus to the centrosomal core. PCNT2 is also involved in the process of normal cell division at the G2-M checkpoint. Thus, loss of PCNT2 likely results in cell death because of defects in both chromosome segregation and mitosis. Rauch et al[6] and Griffith et al[5] have described clinical syndromes associated with biallelic loss-of-function mutations in the gene encoding PCNT2—also termed kendrin (PCNT2 - chromosome 21q22.3-qter - OMIM 605925).

The reason that loss-of-function mutations in PCNT2 result in 2 clinically similar (microcephaly, facial features, growth retardation) but distinct (proportionate versus non-symmetrical short stature, reasonably normal mentation versus developmental delay) disorders of MOPD II or Seckel syndrome is uncertain. It has been suggested that in MOPD II, the PCNT2 mutations may adversely affect function of the centrosome, while in Seckel syndrome the mutations may impair mitotic progression. Life span in primordial dwarfism is around 30 years8 of age, but survival up to 75 years has been reported[2].

Diagnostic criteria: [7]

Association of

- Proportionate dwarfism of prenatal onset
- Characteristic dysmorphic features including severe microcephaly and bird headed like appearance.
- Mental retardation
- Autosomal recessive inheritance.

Diagnosis:[7]

In most cases diagnosis depends on clinical findings. Increased chromosomal breakage has been reported but not in all patients. X-ray features include retarded bone age, dysplasia of the hip and dislocation of the head of the radius.

Antenatal Diagnosis:[7]

Recurrence of the disease can be suspected by observation of intrauterine growth retardation with microcephaly in the second trimester of pregnancy when a first child was born with Seckel syndrome. Linkage studies are difficult to use even in consanguineous families because of the heterogeneity of the disease. Early antenatal diagnosis can be performed for a couple who have had a first child with Seckel syndrome if the familial mutations have been identified.

Complications:[7]

Pancytopenia and acute leukemia have been reported in a few children with Seckel syndrome.

References

1) Weerakkody Y. Seckel Syndrome [Internet] 2010 November 27 [Cited 2012 March 15] Available from: http://radiopaedia.org/articles/ seckel -syndrome

2) Jones KL. Smith's Recognizable Pattern of Human Malformation 6th Ed. Philadelphia: Elsevier Saunders; 2006. Seckel Syndrome; p 108-9.

3) McKusick V A et al. Seckel Syndrome 1 [Internet] 1986 June 3 [Updated 2010 June 9 ;Cited 2012 March 15] Available from: http://omim.org/entry/210600

4) Genetics of Dwarfism [Internet] November 2008 vol24 number 2[Cited 2012 March 15] Available from: www.GGHjournal.com/volume24/2/ toc24-2.cfm

5) Griffith E, Walker S, Martin C-A, et al. Mutations in pericentrin cause Seckel syndrome with defective ATR-dependent DNA damage signaling. Nature Genet. 2008;40:232-6.

6) Rauch A, Thiel CT, Schindler D, et al. Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. Science. 2008; 319:816-9.

7) Faivre L Cormier-Daire V. Seckel Syndrome. Orphanet Encyclopedia [Internet] 2005 April. [Cited 2012 March 15] Available From: http://www.orpha.net/data/patho/GB/uk-Seckel(05).pdf

8) Smith S E, Wallace O. What is Primordial Dwarfism? [Internet]. Available from: http://www. wisegeek.com /what-is-primordial-dwarfism.htm

LDL-C – BAD BOY AT ANY LEVEL?

We all know that a high level of bad cholesterol (LDL-C) is not good for the heart. Keeping this bad boy in check is the therapeutic and dietary goal of every cardiologist. Does it mean that it is good to have a persistently low level of LDL-C? If we are to go by the results of a study presented at the 61st Annual Scientific Session of the American College of Cardiology that is not the case. In that study, Dr. Paul Michael Lavigne and his co-workers from Tufts Medical Center in Boston found that persistently low level of LDL-C (unrelated to intake of cholesterol lowering drugs) increases the risk of cancer. This matched case control study was carried out on 201 cancer patients and 400 cancer free controls. Both groups were also matched by age, gender, tobacco use, blood pressure, body mass index, diabetes, and other factors. They found consistently low levels of LDL-C in cancer patients. Of course, it does not mean that low LDL-C level invariably leads to cancer. For the present, persons with high LDL-C should continue to follow cholesterol lowering guidelines.

http://www.nlm.nih.gov/medlineplus/news/fullstory_123357.html

- Dr. K. Ramesh Rao

Shenbagadevi Falls - kutralam

Case Report

Aesthetic Replacement of Missing Tooth Using Fiber Splint

Dr.Shanmugam.M,* Dr.V.Shivakumar** Dr.R.Saravana Kumar***

Chettinad Health City Medical Journal 2012; 1(1): 31 - 33

Dr.M. Shanmugam M.D.S., is working as a Reader in the Department of Periodontology in Chettinad Dental College & Research Institute for past the 5 years. He graduated from Vinayaka Mission's Dental College, Salem and did his Masters in Periodontics, Ragas Dental College & Hospital, Chennai. He has published widely in national and international journals. He has participated and delivered guest lectures in over 40 national and international conferences. He actively participates in community health services and research oriented programmes.

*Reader, ** HOD & Professor, *** Professor, Chettinad Dental College &Research Institute, Chennai-603103.

Abstract

Missing anterior teeth is of serious concern in the social life of a patient in most of the societies. Conventional fixed partial dentures and implant-supported restorations may often be the treatment of choice. Fiber-reinforced composite (FRC) resins offer a conservative, fast, and cost-effective alternative for single and multiple teeth replacement and may prove to be a successful modality for aesthetic and functional replacement of missing teeth along with periodontally compromised abutments, which has always been a challenge for the dentist. The aim of the case report is to describe the clinical procedure in rehabilitation of edentulous space through fabrication of direct fiber-reinforced composite resin fixed partial denture with periodontal splinting of adjacent teeth.

Key Words: Missing tooth, Replacement, Fiber – reinforced composite splint, Periodontitis.

Introduction

Over the last few years there has always been a challenge to the clinician in aesthetic and fixed replacement of missing anterior teeth, for those patients who cannot have either implant or conventional fixed prosthesis. Factors responsible for such may be abutment teeth prognosis, age and financial or time limitations. Initially, the use of steel wires[1] and wire mesh[2], metal pins, fiber mesh[3] embedded into resins was recommended as more conservative single visit techniques. However these materials had no chemical interactions with composite resins, resulting in clinical failure due to stress concentration when subjected to masticatory forces. To overcome this problem, more resin was used over the reinforcement materials, leading to over contoured restorations which were associated with retention of food and plaque accumulation.

The development of adhesive technique and fiber-reinforced composite (FRC) resins materials has thus provided the chair side approaches for stabilizing mobile teeth and replacing missing teeth conservatively and cost effectively.

When replacing missinganterior teeth, thorough treatment planning is essential. Correct choice of materials and bonding techniques are important factors to fulfill the need for durable restoration without compromising aesthetics of FRC-fixed partial denture. The FRC prosthesis fabricated using two approaches, the first approach is based on conventional tooth preparation and laboratory made restoration, second approach is based on using fibers in minimally invasive restoration by direct or indirect fabrication.

The aim of this case report is to illustrate a technique for aesthetic chair side replacement of missing mandibular tooth through the construction of direct polyethylene fiber reinforced composite fixed partial denture and functional rehabilitation of periodontally compromised abutment teeth.

Case report

A 47 year old lady reported to the department of Periodontics, Chettinad Dental College & Research Institute Chennai, with the chief complaint of unaesthetic appearance and discomfort during function, associated with the mandibular anterior teeth. Patient had lost mandibular left lateral incisor due to advanced periodontal disease (Figure-1). Clinical and radiographic examination revealed that the patient had maximum intercuspal position, moderate bone loss with Grade I tooth mobility in mandibular anterior teeth (according to the Miller index for tooth mobility).

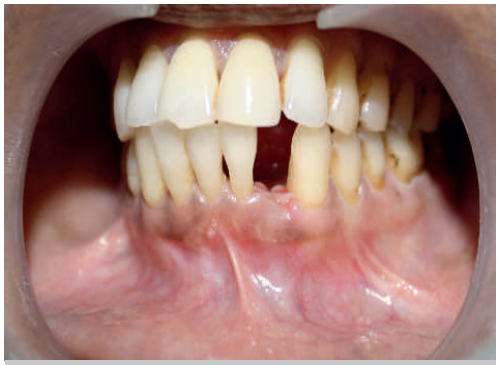


Fig 1: Preoperative view of missing left lateral incisor due to advanced periodontitis

The teeth were scaled and root-planed to assure that all calculus and stains were removed.

After phase-I periodontal treatment the use of direct fixed partial prosthesis with polypropylene fiber reinforced composite was proposed as a quick, economical and, non invasive procedure. This procedure is an alternative to the removable partial denture, resin retained prosthesis and conventional fixed partial denture to rehabilitate the prosthetic space and create a periodontal splint for the abutment teeth.

Procedure

The teeth were cleaned on the facial and lingual surfaces using a prophylaxis cup with a nonfluoridated pumice paste. The length of reinforced fiber (Interlig, angelus) (Figure-2) was determined by placing the dental floss on facial side of the mandibular anterior teeth from distal end of left canine to distal end of right canine. After the teeth were thoroughly rinsed and dried, the lingual surface of teeth to be splinted were etched with 37% phosphoric acid (Dentsply) for 30 seconds. The preparations were rinsed with water and dried leaving the etched surface slightly moist.

Fig 2: Fiber-reinforced composite mesh (Interlig)

A bonding agent (Dentsply) was applied on all the prepared abutments and fiber mesh. The excess bonding agent was removed, a thin layer of flowable composite was applied to the lingual surface of abutment, and the length of polyethylene fiber mesh was carefully placed on the lingual surface of the abutments just above the cingulum, composite was again applied over the fiber mesh. The restoration were polymerized for 30 seconds with light polymerizing unit at 420mw/cm2 from lingual and facial surface of abutment and edentulous space.

Composite pontic was prepared on to the facial aspect of already cured fiber band in the edentulous space. Additional composite resin was applied to blend the FRC contours and light polymerized. Incisal adjustments were accomplished and final finishing and polishing done (Figure-3). Routine oral hygiene instructions were given, the patient was evaluated every 6 months for review and periodontal therapy was observed to be effective in obtaining optimal oral health. Periodontally compromised abutment teeth exhibited signs of periodontal health, patient was highly satisfied with aesthetic and functional outcome of the treatment.

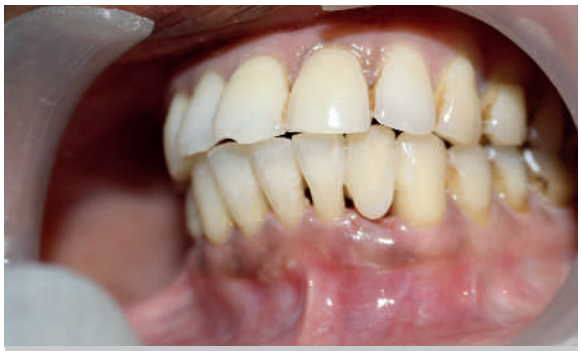


Fig 3: Post operative facial view of rehabilitation of missing tooth with Periodontal splinting

Discussion

This clinical report describes the aesthetic replacement of a missing mandibular left lateral incisor and splinting of periodontally compromised teeth adjacent to the prosthetic space with a conservative FRC-FPD resulting in success over a short-term follow up. This treatment option can be categorized as a periodontal prosthesis[4]. Direct technique is conservative, cost effective, eliminates laboratory procedure. The prosthesis can be placed in a single visit using natural teeth, acrylic tooth or composite resin teeth as a pontic. The aesthetics of the FRC-FPD was shown to be considerably better than the aesthetics of FPDs with metal frameworks, as subjectively determined by many observers[5].

The development of dentin adhesive systems has also led to similar and minimally invasive preparations. But clinical longevity of these prosthesis was found to be poor due to lack of interaction between metals and composite resins, leading to detachment under occlusal forces[6]. In vitro studies have shown that FCR materials exhibit increased strength when compared to particulate resin alone and can withstand occlusal forces in load bearing situations. Vallittu and Sevelius[7] studied clinical success of FRCPs and found 93% survival rate after 24 months follow up. In another study Vallittu et al,[8] showed success rate was to increase from 75% to 95% at 42 months.

Metal framework adhesive fixed prostheses in comparison were found to have 61% survival rate in long term follow up to 11 years. Corrente & Hoppner et al et al[9] studied resin-bonded fixed partial dentures and splints in periodontally compromised patients and the 20 year cumulative survival rate from life table analysis was 76.2% (70.6% for fixed partial denture and 80.7% for splints).

Conclusion

The development of FRC has expanded the possibilities for conservative tooth replacement and tooth /teeth stabilization. This case report describes the clinical procedure using conservative, aesthetic and cost effective FRC-fixed partial denture which splinte the periodontally compromised teeth. Long term clinical studies will be required in the future to provide additional information on the survival and stabilization

of directly bonded fixed prostheses made with polyethylene fiber reinforced composite resin fixed partial denture.

References:

1) Klassman B, Zucker HW. Combination wire composite intercoronal splinting rationale and technique. J Periodontal 1976;47:481-486.

2) Schmid MO, Lutz F, Imfeld T. A new reinforced intracoronal composite resin splint. Clinical result after 1 year. J Periodontal 1979; 50:441-444.

3) Miller TE. A new material for periodontal splinting and orthodontic retention. Compend Contin Educ Dent 1993; 14:800-812.

4) Miller TE, Hakimzadeh F, Rudo DN. Immediate and indirect woven polyethylene ribbon reinforced periodontal –prosthetic splint: A case report. Quintessence Int 1995; 26:267-271.

5) Vallittu PK, Sevelius C. Resin bonded, glass fiber reinforced composite fixed partial dentures: Aclinical study. J Prosthet Dent 2000; 84:413-8.

6) Rudo DN, Karbhari VM. Physical behaviors of fiber reinforcement as applied to tooth stabilization. Dent Clin North Am 1999; 43:7-35.

7) Freilich MA, Meiers JC, Duncan JP. Fiber reinforced composites in clinical dentistry. Chicago: Quintessence; 2000. P. 9-21, 49-63.

8) Hoppner et al, Rehabilitation of periodontal compromised teeth with fiber reinforced composite resin- a case report. Quintessence Int 2011; 42: 113-120.

9) Corrente G, Vergnano L, Re S, et al. Resin-bonded fixed partial dentures and splints in periodontally compromised patients: a 10-year follow-up. Int J Periodontics Restorative Dent 2000 Dec; 20(6) :628-36

FURTHER ATTEMPTS TO RESTORE THE DAMAGED HEART

Following myocardial infarction, the heart fails to regain its original functional capacity even after healing. This is because the cardiac muscle is incapable of regeneration. So, when healing occurs, the dead cardiac muscle fibres are replaced by supportive but non-functional scar. Numerous attempts are being made to restore the normal functionality to the damaged part of the heart. One popular experimental approach has been to use stem cells to replace the fibroblasts in the scar. But so far, no sustained benefit has been achieved with this approach. Another approach appears to be more promising. In a series of studies, Dr. Deepak Srivastava and his associates of Gladstone Institute of Cardiovascular Disease at San Francisco have managed to identify 3 genes (Gata4, Mef2c, and Tbx5) that can transform scar fibroblast into cardiac myocyte. In their latest experimental study in mice, they succeeded in transforming experimentally induced myocardial scar into cardiac muscle in a two-step process. Results of this study appear to hold a great promise for the future management of myocardial infarction. The latest developments were presented at Frontiers in CardioVascular Biology (FCVB) 2012 meeting, held 30 March to 1 April at the South Kensington Campus of Imperial College in London

- Dr. K. Ramesh Rao

Case Report

A Rare Case of Gastric Volvulus With Wandering Spleen

Dr.N.Sivarajan,* Dr. U. Sandeep* Prof. Karunanidhi**

Chettinad Health City Medical Journal 2012; 1(1): 34 - 35

Dr.N.Sivarajan, M.S.(General Surgery), D.L.O, D.Lap, M.B.A.(HSM), F.I.A.G.E.S.

Surgeon who belongs to 1985 batch from MADRAS MEDICAL COLLEGE, Chennai. Did his postgraduate Diploma in ENT and Master degree in General surgery at MMC. Has a Masters in Business Administration(MBA) in Health services Management from ANNA UNIVERSITY, Chennai. Practicing Surgery for the past 21 years. Was a solitary entrepreneur and joined Voluntary health service, Adyar mentoring DNB post graduates in General surgery from 2004 to 2007. Joined Chettinad Hospital and Research Institute in 2007 November as Assistant Professor in General Surgery. Has attended many National conferences and presented interesting clinical cases and studies in General surgery.

*Assistant Professor, Dept. of General Surgery, CHRI **Professor, Dept. of General Surgery, CHRI

Introdution

Gastric volvulus was first described by Berti in 1866 at autopsy on a 60 year old woman who died of closed loop obstruction. Berg,1896 carried the first successful operation of gastric volvulus. First Radiological demonstration was shown by Rosselet,1920. Literature review shows around 200 cases of Gastric volvulus were diagnosed between the period 1920 to 1971. Considering the rarity of this condition, gastric volvulus associated with wandering spleen is even more a rare entity, with only around 5 cases reported in the last decade.

Here we describe this unusual case of an 18 yr old female who presented as acute abdomen, diagnosed with acute organo axial volvulus of stomach with gastric perforation associated with wandering spleen.

Key Words: Gastric volvulus, Wandering spleen, Acute abdomen

Case report

An 18 yr old female presented to the Emergency Trauma Care department of Chettinad Hospital with symptoms and signs of acute abdomen of 1 day duration which was precipitated after consuming food. No history of fever, loose stools or history of trauma. Upper abdominal pain started after consumption of heavy dinner associated with severe retching and scanty vomiting.

Physical examination showed signs of dehydration with stable vitals. The abdomen was warm, tender, guarded and rigid with fullness of flanks which were dull on percussion.

After initial resuscitation, patient was sent for investigations where CT scan abdomen revealed malrotated spleen to right hypochondrium and organo axial malrotation of stomach with intraperitoneal free fluid.

The diagnosis was confirmed and patient underwent emergency laparotomy under general anaesthesia, with the intra operative findings of intraperitoneal contamination of gastric contents with undigested food particles due to tear in the anterior wall of the stomach following closed loop syndrome. Spleen was found to be completely floating in the right hypochondrium due to lack of ligamentous attachments. Eventeration of the left dome of diaphragm was noted.

Thorough peritoneal lavage was done with 3 liters of normal saline and cavity was thoroughly cleaned and the ragged three centimeter perforation was repaired. Splenopexy and gastropexy was done.

Patient had a stormy post operative period with septicemic shock in ICU which was appropriately managed. Her clinical condition improved and she was gradually started on a soft solid diet.

Discussion

Gastric volvulus is defined as an abnormal degree of rotation of one part of the stomach around another. It may be commonly associated with eventration of diaphragm. Most of the cases are mesoaxial and occur with a rotation along the long axis of the gastrohepatic omentum. Diagnostic delay or late presentation results in ischemia, perforation and death.

Wandering spleen is by definition "A mobile spleen that is attached only by an elongated vascular pedicle", allowing it to migrate to any part of the abdomen or pelvis. It is a rare congenital malformation resulting from abnormal development of splenic peritoneal attachments.

The torsion of wandering spleen is more likely in adults at 20-40 years of age due to laxity of ligamentous support as a result of splenomegaly or pregnancy. 15% of children with wandering spleen are asymptomatic, 55% present with abdominal pain, 90% with a mass in the left hypochondrium.

There is a rare association between gastric volvulus and wandering spleen; the two entities share a common cause, i.e. the absence or laxity of intraperitoneal visceral ligaments. Our patient also had the classical eventeration of left dome of diaphragm.

In conclusion the conditions are potentially life threatening if not immediately managed surgically.

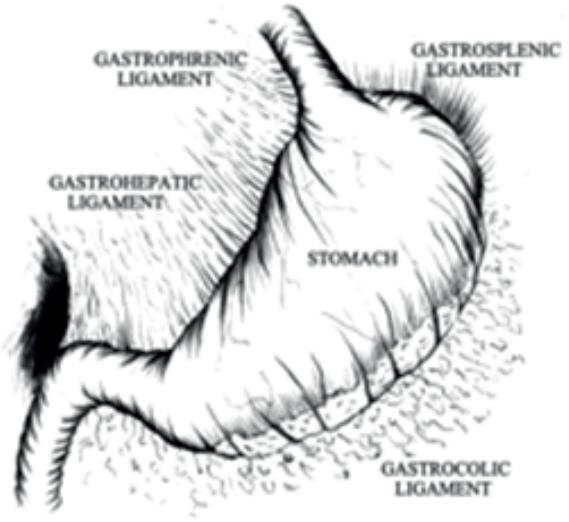


Fig 1. The 4 ligaments of the stomach normally function to prevent twisting or turning about 2 anchor points: the gastroesophageal junction and the pylorus

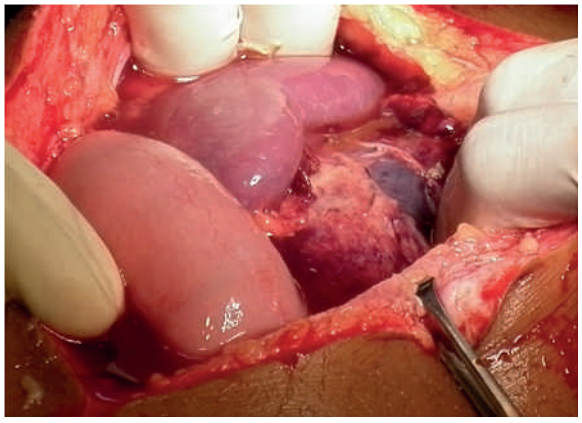


Fig 2. Intra operative picture showing spleen on right side with contamination of peritoneum due to rupture of stomach secondary to closed loop syndrome.

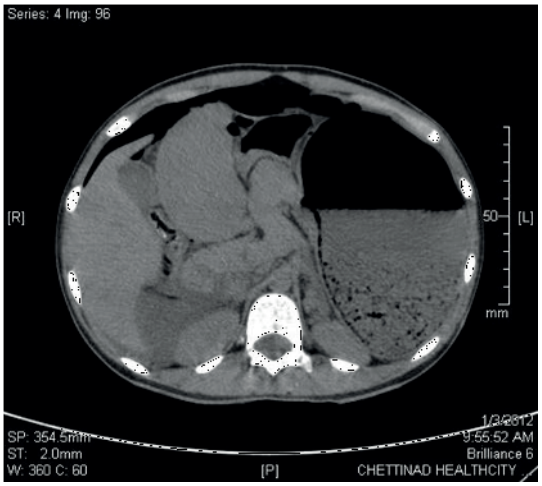


Fig 3. CT Picture showing spleen wandered to the right side besides the liver and gallbladder. Stomach with food contents on the left- organoaxial rotation

References

1) Thompson,J.S, Ronald J Ross & sally. The wandering spleen in infacy and childhood 1980 19:221.

2) Albert A.Nemcek,Jr, Frank H Miller & Steven W.Fitzgerald. Acute Torsion of a Wandering Spleen (1991 August) AJR:157 ;307-309.

3) Mark L Rodkey & Michael L.Macknin.Pediatric wandering spleen: Case report and review of literature (1992 May) 31:289.

4) Daniel L.Miller,MichaelD Pasquale,& Russel P senesa Gastric volvulus in paediatric population (1991, May) Arch surg-vol 126,1146-1149.

Class Room

The Acute Abdomen

Prof. Dr. R. Ganesan,* S. Ramanujam**

Chettinad Health City Medical Journal 2012; 1(1): 36 - 39

"Prof.Dr. R. Ganesan is presently the Head of Department, General Surgery in Chettinad Hospital & Research Institute. He has vast experience in the surgical field and as a teacher in various government institutions spanning over three decades."

*Professor, ** Assistant Professor, Dept. of General Surgery, CHRI

Abstract

The acute abdomen may be defined as an intra- abdominal process causing severe pain and often requiring surgical intervention. It is the most common complaint by individuals attending the outpatient department or the emergency department. In most of the cases, a thorough history and physical examination will reveal the cause of the abdominal pain or at least sufficiently narrow down the possibilities to allow initial treatment decisions to be made. Therefore it is of prime importance that a thorough examination be done both in elective and emergency scenarios.

Causes of the Acute Abdomen

Any pathology in the organs in the abdomen, pelvis and retroperitoneum may cause acute abdominal pain. It may include the following:

Table 1. Causes of acute abdomen

Intra abdominal causes

Perforation

Gastro Intestinal (GI) tract

- Ulcer (Duodenal ulcer/ Gastric ulcer)
- Infection (small intestines in Enteric fever)
- Trauma
- Parasites
- Cancer

Genito Urinary (GU) tract

Inflammation

- Acute Gastritis
- Duodenitis
- Cholecystitis
- Pancreatitis
- Acute Appendicitis
- Acute Salphingitis, etc...

Obstruction

GI tract

- Adhesions
- Hernia
- Volvulus,
- Tumor
- Intussusception
- Parasites

GU tract

- Stone
- Tumor

Vascular System

- Thrombus
- Embolus (mesenteric ischemia)

Hemorrhage

- GI tract
- GU tract

Medical Causes of Acute Abdomen

One should not forget that there are occasions, during which symptoms of acute abdomen may occur in the following medical conditions.

Table 2. Medical causes of acute abdomen

Supradiaphragmatic

- Myocardial infarction
- Pericarditis
- Lower lobe pneumonia
- Pneumothorax
- Pulmonary infarction

Endocrine and metabolic

- Diabetic ketoacidosis
- Addisonian crisis

Hematologic

- Sickle cell disease
- Acute leukemia
- Porphyria

Drugs

Nervous System

- Herpes Zoster
- Tabes dorsalis
- Nerve root compression

The Pathophysiology of Abdominal Pain

It is important for us to know the mechanism behind the distribution of pain fibres within the abdomen and the retroperitoneum, so that the clinical symptoms and signs of acute abdomen can be deciphered. Pain may be mediated by somatic or visceral nerves. In addition patients might have referred pain.

Visceral pain vs somatic pain

During embroyological development, the gastrointestinal tract is divided into three regions based on blood supply and innervation; these relationships are maintained from embryonic to adult life. The foregut consists of oropharynx, esophagus, stomach, proximal duodenum, pancreas, liver, biliary tract, and spleen. The midgut includes distal duodenum (ligament of Treitz), the small intestine, appendix, cecum, ascending colon, and proximal two thirds of the transverse colon. Rest of the colon and rectum make up the hindgut.

The GI tract consists of both somatic as well as visceral peritoneum. Though both of them are continuous, the visceral peritoneum is supplied by the autonomic nerves whereas the somatic peritoneum is supplied by spinal nerves. Therefore visceral pain tends to be vague and poorly localized to the epigastrium, periumbilical region, or hypogastrium, depending on its origin from the primitive foregut, midgut, or hindgut. In contrast, parietal pain corresponds to the segmental nerve roots innervating the peritoneum and tends to be sharper and better localized.

The visceral peritoneum and its associated organs are insensitive to pain caused by touch, electrical stimulation, and cutting or burning; but the sensation of pain from these sites can be induced by stretching, distention of hollow viscus, or vigorous contraction against resistance. Visceral pain usually indicates the presence of significant intraabdominal disease. Extension of the underlying disease process to include the parietal peritoneum is implicated by the transition of visceral pain to somatic pain and often mandates the need for urgent operative intervention (e.g., intestinal obstruction with strangulation). However, somatic pain of intraabdominal origin can be caused by conditions that do not require an emergency surgery (e.g., acute diverticulitis). Therefore it is important to distinguish localized somatic pain from diffuse somatic pain. Although conditions associated with localized peritonitis may require operation, the degree of urgency is far less than in diffuse peritonitis, where an emergency surgery is usually required.

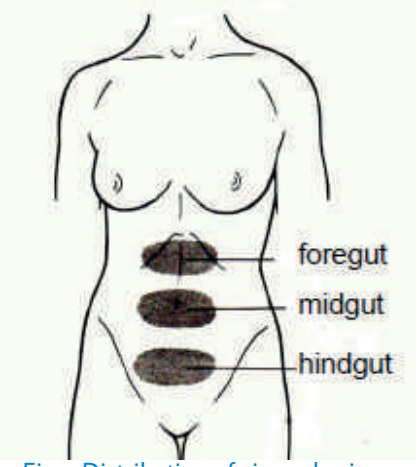


Fig 1. Distribution of visceral pain

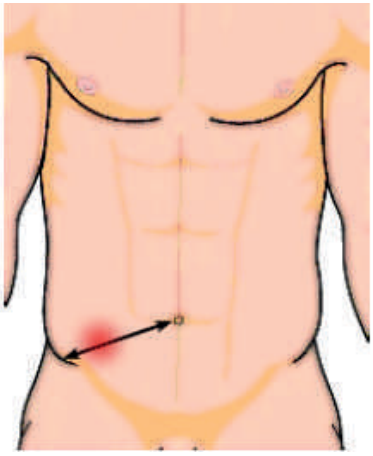


Fig 2. Localised somatic pain

Referred Pain

Apart from somatic and visceral pain, there is another form of pain related to acute abdominal disorders- referred pain. Referred pain is perceived at a site distant from the original location of the pathology but in a region that shares a common embryonic origin. One common example is the radiation of pain from hepatic abscess to the right subscapular region or right shoulder. This is because phrenic nerve is derived from the fourth cervical nerve. Therefore irritation of the undersurface of the right hemidiaphragm, caused by the hepatic abscess may induce pain in the skin distribution of the fourth cervical nerve.

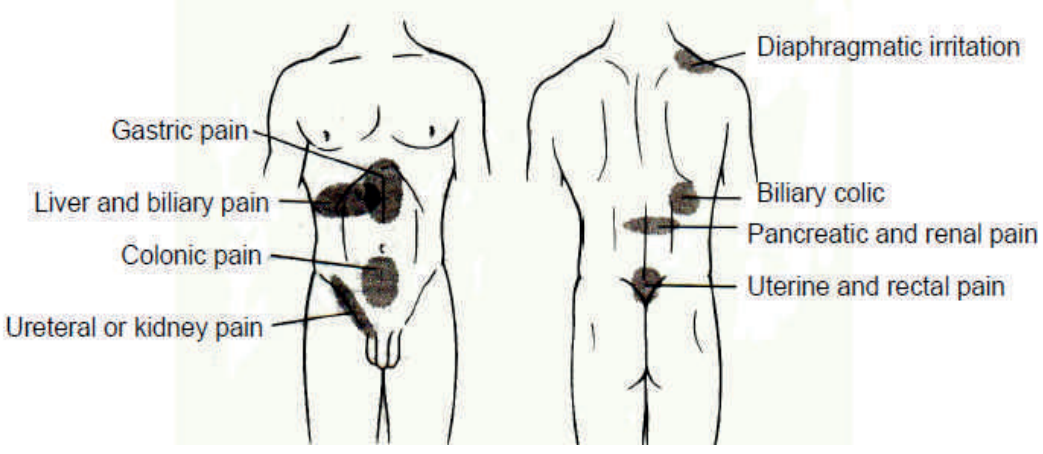


Fig. 3. Referred pain

Clinical Signs and Symptoms

SYMPTOMS reflect a subjective change from normal function which includes pain, anorexia, nausea, vomiting, dysphagia, weight loss, bloating, diarrhea, constipation, flatulence. Duration, intensity, character, radiation and activities that exacerbate or relieve pain should be enquired. Sudden onset of excruciating pain suggests conditions like intestinal perforation or bowel ischemia, though other conditions like biliary colic, can also present as sudden pain. Pain that develops and worsens over several hours usually denotes conditions of progressive inflammation or infection like cholecystitis, colitis, or bowel obstruction. The history of progressive worsening, in contrast to intermittent episodes of pain, can help to differentiate infectious processes from obstruction or colic where spasmodic pain is experienced. Eating generally worsens the pain due to bowel obstruction, pancreatitis, diverticulitis, biliary colic or bowel perforation. Food can relieve pain due to nonperforated peptic ulcer disease or gastritis. Patients with peritonitis avoid any activity that causes sudden body movement or stretch of the abdomen.

Associated symptoms are also important clues to the diagnosis. Vomiting is more likely to precede the onset of significant abdominal pain in most medical conditions whereas the pain of an acute surgical abdomen presents first and stimulates vomiting. Constipation or obstipation results from mechanical obstruction or decreased peristalsis. Diarrhea usually associated with blood can be seen in colonic ischemia.
Taking a careful clinical history and examination will help in planning for investigation and management, like history of alcoholism for pancreatitis, past history of surgery and renal stones and history of missed periods for ruptured ectopic pregnancy.

SIGNS are objective and reproducible findings.Physical examination should begin with general examination including pallor, cyanosis, diaphoresis and vital signs, inspection of patients attitude in bed, and facial expression. Unwillingness to change position indicates underlying peritonitis; these patients lie very still in the bed during the evaluation often maintaining flexion of their knees and hips to reduce tension on the anterior abdominal wall. A patient with acute pancreatitis usually prefers to lean forward.

Auscultation provides us with information about the gastrointestinal tract and the vascular system. A quiet abdomen is found in ileus, whereas hyperactive bowel sounds are heard in enteritis and early ischemic intestine. Bruits reflect turbulent blood flow within the vascular system and indicate stenosis.

Percussion of the abdomen distinguishes gaseous distention from ascites; Tenderness to percussion, either localized or across the abdomen, suggests focal or diffuse peritonitis.

Palpation reveals the presence of warmth, tenderness, guarding, rigidity and the presence of any abdominal mass. Palpation should always be gentle. The patient is informed prior to palpation, and palpation should always start from an area where the patient does not have pain.

Common Diagnosis based on region of abdominal pain

Epigastric	
	Gastritis
	Gastric ulcer
	Pancreatitis
Right hypochondrium	
	Duodenitis
	Acute cholecystitis/cholelithiasis
	Acute hepatitis
	Pneumonia right lower lobe
	Fracture ribs
Left hypochondrium	
	Splenic injury
	Pancretitis (tail)
	Pneumonia left lower lobe
	Fracture ribs
Umbilical	
	Appendicitis (early stage)
	Small intestinal obstruction
	Regional enteritis
Right iliac fossa	
	Acute appendicitis
	Ruptured ectopic
	Pelvic inflammatory disease
	Torsion of testes/ovary cyst
	Ureteric calculus
Left iliac fossa	
	Diverticulitis
	Ruptured ectopic
	Pelvic inflammatory disease
	Torsion of testes/ovary cyst
	Ureteric calculus
Suprapubic	
	Cystitis
	Vesicle calculus
Right and left lumbar	
	Renal calculus
	Nephritis

Investigations

Initial haematologic investigations include haemogram, electrolytes and blood urea. Serum amylase and liver function tests can be done in patients with upper abdominal pain.

A guiding principle in ordering radiologic tests is that the result should substantially influence plans for further testing or therapy. Redundant tests should be avoided1. Plain X ray abomen and X- ray chest in the erect posture to look for free air under diaphragm in case of perforation. Upright chest radiographs can detect as little as 1 mL of air injected into the peritoneal cavity.

Clinical Signs and Symptoms

Abdominal ultrasonography is extremely useful in detecting gallstones, assessing gallbladder wall thickness, diameter of the extrahepatic and intrahepatic bile ducts, more importantly the presence of intraperitoneal fluid. Transvaginal ultrasound aids in the detection of abnormalities of the ovaries, adnexa, and uterus.

Most of the common causes of acute abdomen and their complications are readily identified by CT scanning. CT is also excellent in differentiating mechanical small bowel obstruction from paralytic ileus. Some of the most difficult diagnostic dilemmas can often be identified by CT scans.

Immediate Treatment of Acute Abdomen

Most of the causes of acute abdomen are associated with third space losses. This leads to rapid dehydration with worsening of vitals, especially if the patient has associated vomiting and diarrhea. Therefore intravascular volume resuscitation is of prime importance. Large bore intravenous cannulas should be obtained and fluid resuscitation with isotonic crystalloids should begin. To help assessment of volume status a foley's catheter has to be inserted. Nasogastric tube is mandatory if concern regarding obstruction is present.

Pain and anxiety worsen the tachycardia in most of the patients. Adequate intravenous analgesia is a must. Antibiotics are started if inflammation is suspected. Definitive therapy or procedure will vary with the diagnosis, like emergency laparotomy for perforation, obstruction or inflammation and gangrene. Never should we forget to reassess the patient on a regular basis.

Further reading

1. Sabiston Text book of Surgery, 18th edition.
2. Greenfield's Surgery, Scientific Principles and Practice, 4th edition.

SIT LONGER, DIE YOUNGER!!

Almost all accept that sedentary life style predisposes to a variety of ailments and to prevent that one must lead an active life with regular exercise. But according to a recent study published in the Archives of Internal Medicine, the lead investigator Dr. Hidde Van Der Ploeg from Sydney University claims that sitting for more than four hours in a day can increase risk of early death by 15% even if one leads an active life with regular exercise. Sitting for too long is detrimental because of the absence of muscle contraction that is necessary to clear the glucose and lipids from the blood. Besides, prolonged inactivity reduces the activity of one of the important enzymes involved in the breakdown of lipids in the blood. So, if one wants to live long, one must take every opportunity to stand, take a walk and refuse to sit particularly in front of a television.

- Dr. K. Ramesh Rao

From the pages of History

Medical Emblem: A Tale of Two Symbols

Dr. K. Ramesh Rao, Professor of Pathology, CHRI

Chettinad Health City Medical Journal 2012; 1(1): 40 - 40

Careful observers would have noticed that medical profession is represented by not one but two symbols. Almost all self-respecting professional healthcare organisations have chosen "Rod of Asclepius" while most of the commercial healthcare establishments have opted for "Caduceus". This seeming discord between service and commerce aspects of our profession has infuriated some perceptive commentators. Daniel P. Sulmasy, in particular, has remarked – "It is hard to trust a profession that cannot even get its symbols straight". So, which one of these symbols is the right one? To answer this question, we have to carefully examine the historical evidence.

Rod of Asclepius (asklepian) belonged to god of healing in Greek mythology, Asclepius. He was the son of Apollo and Coronis, and he was instructed in the art of medicine and healing by the centaur Chiron. Asclepius became such a skilled physician that he could bring dead back to life. Many temples were erected in his honour and he was worshipped as god of healing. His staff with an encircled snake has come to symbolize healing and resurrection. However, some commentators have claimed that it is the symbolic representation of the traditional treatment for Guinea worm infestation. His daughters, Meditrine, Hygeia and Panacea became symbols of different branches of health care – medicine, hygiene and healing. Even Hippocrates acknowledged their importance by invoking Asclepius, Hygeia and Panacea in addition to Apollo in his original oath. So, the credentials of Asclepius as a physician and healer are impeccable.

What about **Caduceus?** Well, it was the wand of Hermes, also known as Mercury in Roman mythology. He was god of commerce, trickery, invention, witchcraft and eloquence, and he was also the protector of thieves. How did his wand become medical symbol? Well, in 6th century AD it was used as an emblem of their trade by alchemists. But in 1902, an army officer entrusted with responsibility of replacing Cross with a new medical symbol by Army Medical Corps of U.S. chose Caduceus instead of Rod of Asclepius. It might have been a mistaken identity or ignorance of historical significance or a pre-occupation with visual impact. Whatever! It definitely was an abject capitulation to style over substance. His fateful decision has since been uncritically accepted by large number commercial healthcare establishments in U.S and (not surprisingly) almost all medical colleges in India. Sadly, according Luke Van Orden, "it may be symbolic of how the medical profession has evolved in late twentieth century". So, should we follow their example?

The core committee members of CHCMJ in their collective wisdom feel that the wisdom and the principles of Asclepius should serve the interests of medical profession much better and his staff is the true symbol of the principles healing on which the modern medicine stands. We have decided to display it on the front cover of our Journal. We hope you agree with our decision. If you don't, please let us know.

Instruction to Authors

Chettinad Health City Medical Journal 2012; 1(1): 41 - 42

Chettinad Health City is a peer-reviewed general medical journal published four times a year by Chettinad Academy of Research and Education with the objective of providing an outlet for the following types of scientific communications:

- Reports of original research;
- Interesting case studies;
- Reviews;
- Short communications (research notes).

Besides these, the journal will also carry regular sections like latest medical news, correspondence, classroom, clinical quiz, student seminars, interviews etc. The journal is not restricted to in-house contributions and welcomes scientific communications from other Institutions in India and abroad. However, the journal strongly discourages duplication of data already published in other journals (even when certain cosmetic changes/additions are made). Besides, serialisation of the articles by the same author is not encouraged. Manuscripts must be solely the work of the author(s) stated, must not have been previously published elsewhere, and must not be under consideration by another journal. The journal prioritises reports of original research that are likely to change clinical practice or thinking about a disease. All papers submitted to the journal are subject to peer review process. All accepted papers will be appropriately edited before publication.

The journal follows the **Uniform Requirements for Manuscripts Submitted to Biomedical Journals**, issued by **the International Committee for Medical Journal Editors (ICMJE)**, and **COPE (the Committee on Publication Ethics) guidelines** for the code of conduct for editors.

Editorial Office Contact Information:

SUBMISSION OF MANUSCRIPT

All manuscripts submitted for publication to the IJMR should include the following:

Covering letter

A covering letter should explain why the paper should be published and identify one of the authors as the corresponding author. The corresponding author (or coauthor designee) will serve on behalf of all coauthors as the primary correspondent with the editorial office during the submission and review process. If the manuscript is accepted, the corresponding author will review an edited typescript and proof, and will be identified as the corresponding author in the published article. The corresponding author is responsible ensuring that the Acknowledgment section of the manuscript is complete.

Manuscript including tables and panels

Manuscripts (including correspondence letters) should be submitted by e-mail/ CD/DVD as a MS Word document in addition to a hard copy. The hard copies should be typed/printed in one and half space on one side of a good quality A4 bond paper (21.0 x 29.7 cms). Pages should be numbered consecutively. Typescript should be sent to the Editor, JCHRI. Authors are advised to see a recent issue of the journal to get familiar with the format adopted on various elements of a paper.

Formatting

All research papers (basic science, clinical trials etc.) should

(1) Be not more than 3000 words with 30 references

(2) Include the elements arranged in the following order:- Title; Name(s) of the author(s); Department(s) and Institution(s); Abstract; Key words; Introduction; Material & Methods; Results; Discussion; Acknowledgement; and References. Abstract, Tables and legends for Figures should be typed on separate sheets and not in continuation of the main text.

(3) The Title of the article should be short, continuous (broken or hyphenated titles are not acceptable) and yet sufficiently descriptive and informative so as to be useful in indexing and information retrieval. A short running title not exceeding 6-7 words may also be provided.

(4) The Abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 300 words. It should only highlight the principal findings and conclusions so that it can be used by abstracting services without modification. Conclusions and recommendations not found in the text of the articles should not be inserted in the Abstract. A set of suitable key words arranged alphabetically may be provided.

(5) The Introduction should be brief and state precisely the scope of the paper. Review of the literature should be restricted to reasons for undertaking the present study and provide only the most essential background.

(6) In Material & Methods, the nomenclature, the source of material and equipment used, with the manufacturers' details in parenthesis, should be clearly mentioned. The procedures adopted should be explicitly stated to enable other workers to reproduce the results, if necessary. New methods may be described in sufficient detail, indicating their limitations. Established methods can be just mentioned with authentic references and if there are significant deviations, reasons for adopting them should be given. While reporting experiments on human subjects and animals, the ICMR's Ethical guidelines for biomedical research on human subjects (2000) should be adhered to. Similarly, for experiments on laboratory animals the guidelines of the Committee for the Purpose

of Control and Supervision of Experiments on Animals (CPCSEA) should be followed. The drugs and chemicals used should be precisely identified, including generic name(s), dosage(s) and route(s) of administration. The statistical analysis done and statistical significance of the findings when appropriate should be mentioned. Unless absolutely necessary for a clear understanding of the article, detailed description of statistical treatment may be avoided. Articles based heavily on statistical considerations, however, need to give details particularly when new or uncommon methods are employed. Standard and routine statistical methods employed need to give only authentic references.

(7) In Results, only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. The data should be arranged in unified and coherent sequence so that the report develops clearly and logically. Data presented in tables and figures should not be repeated in the text. The same data should not be presented both in tabular and graphic forms. Interpretation of the data should be taken up only under the Discussion and not under Results.

(8) The Discussion should deal with the interpretation of results without repeating information already presented under Results. It should relate new findings to the known ones and include logical deductions. It should also mention any weaknesses of the study. The conclusions can be linked with the goals of the study but unqualified statements and conclusions not completely supported by the data should be avoided. Claiming of priority on work that is ongoing should also be avoided. All hypotheses should, if warranted, clearly be identified as such; recommendations may be included as part of the Discussion, only when considered absolutely necessary and relevant.

(9) Acknowledgment should be brief and made for specific scientific/technical assistance and financial support only and not for providing routine departmental facilities and encouragement or for help in the preparation of the manuscripts (including typing or secretarial assistance).The corresponding author must obtain written permission from each person named in the Acknowledgment section and must be willing to provide the editors with copies of these permissions if requested to do so. The corresponding author must sign the Acknowledgment statement part of the Authorship Form confirming that all persons who have contributed substantially but who are not authors are identified in the Acknowledgment section and that written permission from each person acknowledged has been obtained.

(10) The total number of References should normally be restricted to a maximum of 30. References to literature cited should be numbered consecutively and placed at the end of the manuscript. In the text they should be indicated as superscript at the end of the line. As far as possible mentioning names of author(s) under references should be avoided in text. The titles of the journals should be abbreviated according to the style used by the Index Medicus.

(11) All image formats (jpeg, tiff, gif) are acceptable; jpeg is most suitable

The references should be in Vancouver style—e.g.,

- Smith A, Jones, B, Clements S. Clinical transplantation of tissue-engineered airway. Lancet 2008; 372: 1201–09.
- Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: Elsevier, 2008: 230–47.

Case reports should present a diagnostic conundrum, and explain how it was solved. Case reports should

- not be more than 1000 words with 10 references
- Include the clinical presentation, history, examination, investigations, management, outcomeand comments/discussion.

Size 8.5" X 11"

Partners of choice in infertility treatment

Down Regulation | Ovarian Stimulation | Ovulation Triggering | Luteal phase Support

Day 3 | Day 11 | Day 14

Gonapeptyl™ Triptorelin 0.1 mg / ml in 5 ml vial

Menopur™ menotrophin (HP-hMG, 75 I.U.)

Koragon™-HP

℞ GESTONE™ Caps

℞ Decapeptyl® Depot TRIPTORELIN - 3.75mg INJ.

℞ Menogon® (HMG, 75 I.U.)

℞ Decapeptyl® 0.1 TRIPTORELIN - 0.1 MG ; READY-TO-USE SYRINGE

℞ GESTONE™ Inj.

Bravelle™ Urofollitropin

Extending support at every stage

FERRING IN PHARMACEUTICALS

FERRING PHARMACEUTICALS PRIVATE LIMITED
403 / 404, Sigma, Technology Street, Hiranandani Gardens, Powai, Mumbai 400 076.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only