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Illustrations and tables should not be inserted in the appropriate place in the text but should be included at the end of the paper, each on a separate page. Tables should be given in Roman numbers (e.g. Table I), and their desired position in the text should be indicated. All photographs, graphs and diagrams should be referred to as Figures and should be numbered consecutively in the text in Arabic numerals (e.g. Figure 2).

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Editorial

Writing Editorials for Medical Journals

Waheeda Nargis[1], Nayeem-Al-Imam[2], Mohammad Liakat Ali[2], Mahfuza Nasrin[2], Syed Faheem Shams[2], Debashis Biswas[2]

'What is an editorial? Who can write or are authorized to write editorials? What to write in and/or how to write an editorial for a medical journal? Are there any standard sets of rules or certain essential attributes to be maintained? ' - very often these genuine yet less frequently addressed queries become barriers between the potential authors' participation and the journal's manuscript turnover. Continuing to publish journal regularly with limited collection of articles during the last two years; in a time of pandemic has been a challenge that the JUAMC editorial team is still struggling to overcome. Experiencing the urgency while managing the crisis, this editorial has been undertaken as an attempt to clarify above issues.

Generally, editorials are supposed to share views and opinions of the editors of the journal primarily focusing on the journal policy or any current issue requiring discussion. According to JAMA, the *Journal of the American Medical Association*; "Editorials in medical journals are short essays that express the views of the authors, often regarding a research or review article published in the same issue. Editorials provide perspective on how the current article fits with other information on the same topic."[1]

Good editorials address current needs. Typically, editorial board assesses and weights which issues are important, beneficial and relevant for their readership. However , in scholarly publishing community, editorial articles are expected to be thought provoking, 'opinion maker'[2], insightful at the same time entertaining enough to interest, motivate & encourage readers to contribute more in ground research on its highlighted themes[3].

Box 1. Purposes of an editorial [adapted from *Peh WCG*[3]]:

- Personal message from the editor to journal readers.
- Commentary on a published article in the same issue.
- Concise review on a topic of current interest (not warranting a full invited review).
- Drawing readers' attention to very recent developments or innovations.
- Commentary on non-scientific topics, e.g. health policy, economics, law or ethics.

Previously, as implied by the term 'Editorial', the editorial message was written by the editor himself. Currently, in the majority of scientific journals, editorials have evolved to serve many other purposes, from critical analysis of original articles published in the same issue to mini- reviews, very recent or global issues, even prospective ideas with promising future-outcomes that are deemed by the editorial team to be appealing to readers of the journal and the community, composed by anyone. Hence, editorials may be written by the editor or someone invited by the editor. Some editorial boards are also found to be considering proffered submissions[4].

Unlike original articles, editorials **do not** follow the IMRAD structure for manuscript organization. There is usually no abstract, subheadings, or a formal conclusion section. There are prescribed limits to the number of words (typically 450–1,000), number of references (20 or fewer) and figures and/or tables (none or up to two)[3,5].

Box 2. IMRAD stands for[6]:

Introduction	(What question was asked?)
Methods	(How was it studied?)
Results	(What was found?)
And	(What do the findings mean?)
Discussion	(What question was asked?)

As editorials may not have abstract, keywords, or sub-sections, their title and the core body becomes the primary concern. Thus, crafting a catchy title which can instinctively draw readers' attention and reflects the essence of the article content is crucial in sustaining reader's attentiveness[7]. However, short, clear and straight-forward titles can also be made as compelling as the intriguing ones which are often more likely to be appreciated by the readers due to their simplicity.

Most editorials do not exceed two printed journal pages in length, so the challenge is to compress the author's message into a rather closed space, and yet presenting ones' ideas in a clear, logical sequence[4].

As per the bold recommendation of Editor in Chief of the Journal of Medical Science & Technology 'the three "S"es of article writing - short sentences, short paragraphs, and simple English' may be integrated in editorials to ensure "much more readable results"[8].

At the end, Editorials are expected to be short, precise and concise with a captivating, self-explanatory title. However, the length and format of editorials can vary widely by different medical journals. It may be considered to be successful one, when it contains the elements of critical argument ideally supported by evidence with a clear and convincing conclusion.

Hope this editorial fulfills the same.

(J Uttara Adhunik Med Coll. 2020; 10(1) : 1-2).

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Original Article

Familial Characteristics and Behavior of the Street Children in Dhaka, Bangladesh

Bushra Zaman[1], Mir Mahmud Hossain[2], Anis Ahmed[3], Azreen Momen Chowdhury[1], Tarana Chowdhury[4]

Abstract

Background: *During the recent decades, facing with irregular and troubled children in a busy street has attracted the community. Thousands of street children of Dhaka city are being addicted to various drugs due to their availability in the capital, leading to an increase in street crimes.*

Objective: *The objective of the study was to find out the familial characteristics of street children of Dhaka city, Bangladesh.*

Materials and Methods: *A cross sectional study was done among 132 street children of selected area of Dhaka city to find out the familial characteristics of street children for a period of July 2018 to December 2018. Data were collected by face to face interview using pre-tested questionnaire and non-parametric Chi square tests (x^2) were done to find out any significant association. The analysis was done by computer using Statistical Package for Social Science (SPSS) version 22.0.*

Results: *The result showed that more than half of the respondents (56.8%) were between the age group of 10-14 years and the mean & SD of age was 13.53±1.41 year. Regarding religion 90.9% were Muslims and the rest 9.1% were Hindu. Majority (88.6%) of the respondents were male. About 40.9% of the respondents had primary education and 31.8% were dropped out from school. Near about 55% were children on the street and 45.0% were children of the street. Majority (52.3%) of the respondents lived in the street for >12 months and 50.0% lived with peer group. About 63.6% of the respondents were earning <100 tk per day and 36.4 % were earning >100 tk per day. About 29.5% of the respondent's both parents were alive. Nearly 70.5% of the respondent's father and 86.4% of the respondent's mother was illiterate. The total monthly family income of most of the families (70.5%) was in the range of 5001-10000 taka and the mean was 5220.50±1724.63 taka. Majority of the respondents (72.7%) were working throughout the year constantly and about 9.1%, 22.7%, 4.5%, 15.9%, 20.5%, 20.5% & 6.8% were street hawker, selling newspaper/water bottle/candy/tea-coffee, bus conductor/tempo helper, beggar, porter/colli, collecting bottle/ plastic and shoe polisher respectively. About 63.6% of the respondents did not handed their earnings to their families and 75% having family contacts. About 47.7% of them were involved in stealing and majority (79.5%) of the respondent's age of first crime conducted was between 10-14 years. The association between the gender with the education of the street children was statistically significant (P<0.007).*

Conclusion: *Street children comprise a significant proportion of the total population. Our study revealed that the street children are fully deprived of their basic necessities leading to an inhuman life. Majority of them were male and engaged in various anti-social activities to get money for purchasing drugs. The situation is very alarming. A comprehensive campaign is needed to deal with drug problems.*

Keywords: *Familial characteristics, Behavior, Street children.*

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Introduction

Rapid urbanization and large scale migration of people to the cities has resulted in the emergence of street children. The most common definition of a street children is "any girl or boy who has not reached adulthood, for whom the street has become her or his habitual abode and/or source of livelihood and who is inadequately protected, supervised or directed by responsible adults"[1].

Millions of children in the world are forced to seek survival on the streets of cities[2]. They work and live alone without adequate food, shelter, education, affection and social security, leaving them extremely vulnerable with many of their physical, mental and social needs unfulfilled[3]. According to UNICEF, there are more than 500,000 street children in India who live and work in inhuman conditions and are at high risk of substance use[4]. According to a survey carried out by ICDDR,B and Most at-Risk Adolescents (MARA) in 2016, there are 4.45 lakh street children in Bangladesh – 3 lakh in Dhaka alone[5]. Around 1,000,000 children are believed to be on the streets of Egypt[6]. The Indian Embassy has estimated that there are 314,700 street children in metros such as Bombay, Calcutta, Madras, Kanpur, Bangalore and Hyderabad and around 100,000 in Delhi alone[7].

The Asia-Pacific region is home to nearly half of the world's children, including large numbers of street-children. Children aged 5–17 years constitute 32% of the total population (about 42 million) in Bangladesh, a poor country of South Asia. There are about 445,226 street-children in Bangladesh at present, and the number is continuously rising; of them, 75% live in the capital city Dhaka; 53% are boys and 47% are girls. It is projected by UNICEF that the number of street-children will grow to 1,615,330 by 2024 in Bangladesh[8]. In the cities, street-children are mostly found near railway stations, launch/boat terminals, bus stations, busy markets, commercial areas, parks/ pavements, big mosques, and *mazar*s (mausoleum)[9-12]. About 45% of children live with parents while a good proportion of them live alone (22%). Although they work 6.5 hours per day, they earn only 45 BDT (1 US$ = 79 BDT) a day[13].

The causes of living on the street included poverty or hunger (89%), running-away from home (14%), torture by step mother/father (11%), earning money or income (11%), lack of guardians to look after (9%), and abuse (6%)[13,14].These children are usually deprived from basic human rights and have inadequate access to food, clothings, accommodation, education, and health facilities[15]. At very early ages, mostly at the age of 7 years, they get involved with different types of profession, such as helping hand of carpenters, hotel/restaurant boy, transport helper, household maid, shoe-shiner, and factory worker[16].

UNICEF has divided the street children into three groups: 1. Children who are away from family and live on streets; 2. Children who work on streets, spend a lot of time on streets, but come back to home regularly; and 3. Children who live with their families on streets. United Nations International Children's Fund (UNICEF) estimates that 100 million of such children live throughout the world, but some of the statistics have estimated this number to be 150 million. According to Andres-Lemay et al., street children were mainly of atypical families and 78% of them had single parents or no parents at all. Furthermore, in UNICEF study in Ethiopia, 23% of street children lived with both parents and in Brown's study in Jamaica, 7% lived with their both parents. Various factors such as economic pressures, unequal distribution of wealth, lack of social services, AIDS and civil wars are effective in the incidence of the phenomenon of street children. Other effective factors also include discrimination, abuse, family violence, drug use, loss of parents, low parental education, and immigration[17].

Taking these facts into consideration and realizing the need for community based data, the present study on the familial characteristics of street children in Dhaka city, was undertaken with the objectives to study the socio-demographic profile of street children.

Materials and Methods

This cross sectional study was done among 132 street children aged from 10-19 years who working on street with or without family ties to find out the familial characteristics of street childdren. The study was conducted at some selected area of Dhaka city like Airport railway station, Cantonment railway station, Kamlapur Railway station and Mohakhali bus terminal for a period of 6 months from July 2018 to December 2018.

The sampling method of the study was purposive sampling. The participants who had consent and willing to participate in the study voluntarily were selected for this study. Research instrument was an interviewer administered questionnaire. The collected data were processed, compiled and analyzed by computer using SPSS version 22.0. The results were expressed in descriptive statistics as frequency, percentage, mean and standard deviation in tables and figures. Non-parametric Chi square tests were done to see any significant association. For all statistical analysis, p-values less than 0.05 were considered significant.

Results

The study was carried out to find out the familial characteristics and behavior of the street children aged 10-19 years of selected area of Dhaka city.

Table I

Socio-demographic profile of the respondents (n=132).

Variables	Frequency	(%)	Mean±SD
Age			
10-14 years	75	56.8	13.53±1.41
15-19 years	57	43.2	
Gender			
Female	15	11.4	
Male	117	88.6	
Religion			
Muslim	120	90.9	
Hindu	12	9.1	
Education			
Illiterate	36	27.3	
Primary education	54	40.9	
Secondary education	12	9.1	
Never been to school	30	22.7	
Drop out from school	42	31.8	
Length of working time			
Working throughout the year	96	72.7	
Occasional worker	36	27.3	
Earning handed to family			
Yes	48	36.4	
No	84	63.6	
Having any family contact			
Yes	99	75.0	
No	33	25.0	

Table I showed that majority of the respondents (56.8%) were between the age group of 10-14 years and 43.2% were between the age group of 15-19 years. The mean and SD of the age of the respondents were 13.53±1.41 years. About 11.4% of the respondents were female and 88.6% were male. Regarding religion 90.9% of the respondents were Muslims and the rest 9.1% were Hindu. Educational status of the respondents showed that 40.9% of the respondents had primary education, 27.3% illiterate, 22.7% never been to school and the rest 9.1% had secondary education. About 68.2% were not dropped out from school and 31.8% were dropped out from school. Majority of the respondents (72.7%) were working throughout the year constantly and the rest 27.3% were working occasionally. About 63.6% of the respondents did not handed their earnings to their families and the rest 36.4% handed their earnings to their families. About 75% of the respondents having family contacts and 25% did not have any family contact.

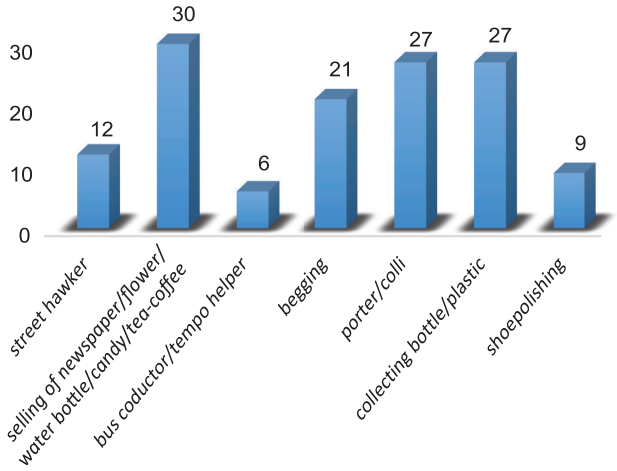

Figure-1: *Distribution of the respondents according to their work (n=132).*

Figure-1 showed that about 9.1%, 22.7%, 4.5%, 15.9%, 20.5%, 20.5% and 6.8% of the respondents were street hawker, selling newspaper/water bottle/ candy/tea-coffee, bus conductor/tempo helper, beggar, porter/colli, collecting bottle/ plastic and shoe polisher respectively.

Table II

Socio-economic profile of the respondents (n=132).

Variables	Frequency	(%)	Mean ± SD
Living with			
Parents	51	38.6	
Grandparents	12	9.1	
Siblings	3	2.3	
Peer group	66	50.0	
Duration of street life			
<3 months	18	13.6	
3-6 months	24	18.2	
6-12 months	21	15.9	
>12 months	69	52.3	
Money earned per day (Tk)			
<100	84	63.6	
>100	48	36.4	92.45±1.84
Type of family			
Nuclear	87	65.9	
Joint	45	34.1	
Family members			
2-4	45	34.0	5.74 ± 1.51
5-7	87	66.0	
Monthly family income (Tk)			
<5000	21	15.9	5220.50±
5001-10000	93	70.5	1724.63
10001-15000	18	13.6	

Table II showed that 38.6% of the respondents were living with their parents, 9.1% with grandparents, 2.3% with siblings and 50.0% with peer group. Nearly 13.6% of the respondents lived in the street for < 3 months, 18.2% for 3-6 months, 15.9% for 6-12 months and 52.3% of the respondents lived in the street for > 12 months. Majority of the respondents (63.6%) were earning <100 tk per day and about 36.4 % of the respondents were earning >100 tk per day. About 65.9% of the families of the respondents were nuclear and the rest 34.1% of the families were joint. Nearly 34.0% of the respondents family were consisted of 2-4 members, 66.0% were consisted of 5-7 members. The total monthly family income of most of the families (70.5%) was in the range of 5001-10000 taka and the mean monthly family income was 5220.50± 1724.63 taka.

Figure-2 showed the living status of the respondents. About 55% were children on the street and 45.0% were children of the street. Children working on the street but maintaining more or less regular ties with their families are mention as children on the street. Children of the street maintain only tenuous relations with their families, visiting them only occasionally.

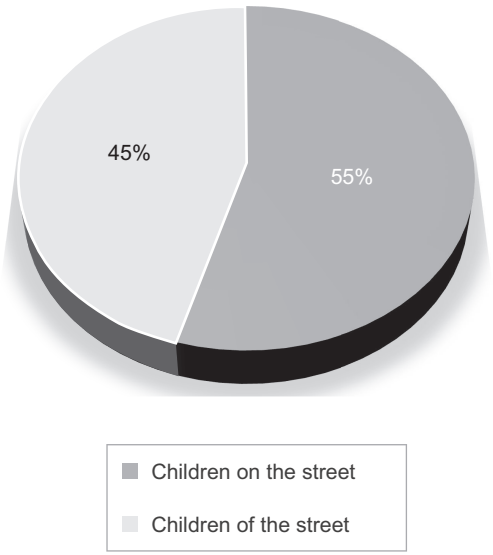

Figure-2: *Living status of the respondents (n=132).*

Table III

Parents profile of the respondents (n= 132).

Variables	Frequency	(%)
Parental characteristics		
Death of father	36	27.3
Death of mother	15	11.4
Death of both parents	21	15.9
Presence of step father	9	6.8
Presence of step mother	12	9.1
Both parents alive	39	29.5
Father's education		
Illiterate	93	70.5
Primary education	27	20.5
Never been to school	12	9.0
Mother's education		
Illiterate	114	86.4
Primary education	3	2.2
Never been to school	15	11.4
Father's occupation		
Garment's worker	15	11.3
Rickshaw/Van puller	42	31.8
Tailor	6	4.5
Newspaper seller	15	11.4
Day labourer	24	18.2
Mason	21	15.9
Bus driver	9	6.8
Mother's occupation		
Housewife	33	25.0
Garment's worker	21	15.9
Tailor	15	11.4
Bua/Maid	33	25.0
Day labourer	15	11.4
Cleaner	15	11.4
Total	132	100.0

Table III showed that 29.5% of the respondent's both parents were alive and the father of 27.3% of the respondents were passed away. About 70.5% of the respondent's father was illiterate, 20.5% had primary education and only 9.0% of the respondents were never been to school. About 86.4% of the respondent's mother was illiterate, 2.2% had primary education and 11.4% of the respondents were never been to school. Regarding the occupation of the respondent's father about 11.3% were garment's worker, 31.8% , 3.8% physician, 1rickshaw/van puller, 4.5% tailor, 11.4% newspaper seller, 18.2% day labourer, 15.9% mason and 6.8% were bus driver. Almost 25% of the respondent's mother were house wives, 15.9% garment's worker, 11.4% tailor, 25.0% bua/maid, 11.4% day labourer and 11.4% were cleaner.

Table IV

Association between gender of the respondents with the age, education and religion of the street children (n=132).

Parameters	Gender		Value of Chi-square test	P-value
	Female No (%)	Male No (%)		
Age (yrs)				
10-14 years	9 (6.81)	66 (50.00)	5.788	0.380
15-19 years	6 (4.54)	51 (38.63)		
Education				
Illiterate	3 (2.27)	63 (47.72)	6.092	0.007
Literate	12 (9.09)	54 (40.90)		
Religion				
Islam	11 (8.33)	105 (79.54)	1.692	0.096
Hindu	4 (3.03)	12 (9.09)		

Association between gender of the respondents and the age, education and religion the street children were shown in Table-IV. The relation between the gender with age and religion of the respondents were not statistically significant. The association between the gender of the respondents with the education of the street children was statistically significant (P<0.007).

Discussion

Street children constitute a socially marginalized set of population who are very difficult to approach. This study provides an overview of the socio-demographic, socio-economic, parents profile and anti-social activity the street children of Dhaka city.

The study was carried out to find out the familial characteristics of the street children aged 10-19 years of selected area of Dhaka city. Majority of the respondents (56.8%) were between the age group of 10-14 years and 43.2% were between the age group of 15-19 years. The mean & SD of the age of the respondents was 13.53±1.41 year. About 11.4% of the respondents were female and 88.6% were male. Study conducted in Pokhra Nepal documented that majority (68.8%) of the street children were between 11 and 15 years of age, with male dominance (95.8%)[18]. In another study by Rane and Shroff on street children in major cities in India, 40% children belonged to age group of 11 to 15 years and 33% belonged to age group of 6 to 10 years of age[19]. Regarding the socio-economic profile of the respondents 65.9% of the families of the respondents were nuclear and the rest 34.1% of the families were joint. Nearly 34.0% of the respondent's family were consisted of 2-4 members, 66.0% were consisted of 5-7 members. Majority of the respondents (63.6%) were earning <100 tk per day and about 36.4 % of the respondents were earning >100 tk per day. The total monthly family income of most of the families (70.5%) was in the range of 5001-10000 taka and the mean monthly family income was 5220.50± 1724.63 taka. It a study of India it was found that vast number of children belong to low income group families, with income of less than rupees 600 per month[19].

A study conducted Pagare in Delhi where he found that these children were of the age group between 8 - 18 years. 76.7 % of these children stayed on the streets in Bangalore even though some children had their families living close to them[20].

In a similar study in Bangalore found that 69% of these children preferred to be on the streets and 24 % hailed from economically poor families. 81.9% of these children were male and earned up to 150 rupees a day. Majority of them were engaged in substance abuse to feel happy, and felt it as form of relief from various problems. They started with tobacco, solvents and proceeded to use of cannabis and alcohol[21]. About 40.9% of the respondents had primary education, 27.3% illiterate, 22.7% never been to school and the rest 9.1% had secondary education. About 68.2% of the respondents were not dropped out from school and 31.8% were dropped out from school. In a study by Xavier and Arulraj, at Chennai, 34% street children

had no schooling, 44 % had studied up to V, 21 % had studied up to X and only 1 % had education of XI and above[22].

The present study reflects that around 55% were children on the street and 45.0% were children of the street. 13.6% of the respondents lived in the street for <3 months, 18.2% of the respondents lived in the street for 3-6 months, 15.9% of the respondents lived in the street for 6-12 months and 52.3% of the respondents lived in the street for >12 months. Near about 38.6% of the respondents were living with their parents, 9.1% with grandparents, 2.3% with siblings and 50.0% with peer group. In one study in Nazareth (Ethiopia), 54.6 % of children were 'on' the street type with a house to sleep at night and 45.4 % were 'of' street type and completely homeless[23].

Majority of the respondents (72.7%) were working throughout the year constantly and the rest 27.3% were working occasionally. About 9.1%, 22.7%, 4.5%, 15.9%, 20.5%, 20.5% and 6.8% of the respondents were street hawker, selling newspaper/water bottle/ candy/tea-coffee, bus conductor/tempo helper, beggar, porter/colli, collecting bottle/ plastic and shoe polisher respectively. About 75% of the respondents having family contacts and 25% did not have any family contact.

Conclusion

The street children face a variety of personal problems at their homes and at work. They are exposed to a variety of risk factors which leads to develop many anti-social behavior on the streets that push these children into substance abuse. Majority wanted to become somebody in life and almost all were willing to take help for their better future. This underlines the need for enriched environment that will prevent further damage to these lives and will lead them to bright future.

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Original Article

Disease Activity of Rheumatoid Arthritis (RA) among Patients Visiting Outpatient of a Tertiary Care Hospital Over One Year – A Prospective Observational Study

Maruf bin Habib[1], Iffat Ara Akbar[2], Faisal Mohammed Pasha[3], Fahim Rahman[4], Humayra Sultana[4], Faysal Ahmed[4]

Abstract

Background: *Rheumatoid Arthritis is an auto-immune disorder that primarily affects joints and can lead to extra articular manifestations causing disability and even death. The treatment for this disease proves to be exorbitant for the people of Bangladesh as they are unaware of proper treatment seeking. The aim of this study is to establish the disease profile of the patients residing in Bangladesh and evaluate the disease activity of Rheumatoid Arthritis.*

Methods: *This prospective observational study has been carried out among 55 patients suffering from Rheumatoid Arthritis aged between 21-70 years. The patients were treated with the same therapeutic protocol using DMARD methotrexate and steroid depending upon the case and were followed up for 1 year. Some of these patients were also given 2nd DMARD (either biologic or synthetic) on the merit of their disease severity. The data are collected from proper history taking, biochemical markers and clinical parameters. Disease activity of Rheumatoid Arthritis was measured by Disease Activity Score-28 (DAS 28). Disease activity and response totherapy were measured at 6 and 12 months. Quality of data was strictly maintained and ethical issues were properly maintained in all the steps of this study.*

Results: *Fifty five patients visiting the tertiary care hospital between January 01 to December 31, 2019 were included in this study. The cohort included 45 (81.9%) women and 10 (18.1%) men, and the mean age of disease duration was 6.90 years (SD 3.38). In the biochemical markers recorded at baseline, mean value of ESR was 62.2 mm in 1sthour (SD 29.7) and CRP was 29.83 mg/dl (SD 5.84). RA test was found to be positive in 34 (61.8%) patients. The number of respondents found to have a high disease activity at the start of the study was 18 (32.7%). The score of DAS 28 showed a decline over the period of 1 year from 4.69 to 3.23.*

Conclusion: *The study provided information concerning some of the profile and the course of Rheumatoid Arthritis in Bangladesh. Gad patients have a good prognosis and responded well to the therapeutic protocol in one year of treatment.*

Key words: *RA (Rheumatoid Arthritis), DAS 28 (Disease Activity Score-28)*

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Introduction

Rheumatoid arthritis is one of the most common rheumatological diseases. It is a chronic autoimmune disease which is characterized by joint involvement and systemic features, leading to a progressive disability and early death[1]. It affects approximately 1% of the population, with higher prevalence in women. Although its etiology is still unknown, it has been theorized that in genetically susceptible individuals environmental factors trigger an autoimmune response

resulting in synovial hypertrophy and chronic joint inflammation and destruction associated with potential extra-articular manifestations[2].

Patients of RA typically experience progressive disability and joint destruction, which occur over 10–20 years. This chronic disease requires long-term treatment, with durable clinical and radiographic benefits[3]. The aim of this study was to highlight the profile of RA patients in a developing Asian country like Bangladesh and also to evaluate the progression of disease using DAS 28 by providing the patient with the standard protocol treatment.

In all chronic diseases, a number of factors predict poor outcome. These include the severity of the disease itself, late presentation, multiple health problems i.e. comorbidities, poverty and old age[4]. The same is seen in RA, in which severe arthritis with multiple joint involvement[4], rheumatoid factor (RF) positivity[5,6], high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)[7], and nodules all predict poor outcome. Other accepted predictors of poor outcome include slow onset, co-morbidities, onset in old age and female gender[4].

Bangladesh is a developing country with a Gross National Income (GNI) of just over 2000 USD[8] which prevents many patients to keep up with the cost involved in the disease treatment.In addition, the patient usually seeks out many specialties for the relief of pain namely Internal Medicine specialists, Rheumatologists and Orthopedic surgeons which result in incomplete or sub-standard treatment due to the following of different guidelines.

As there is no definitive cure for this disease, it is important to prevent the complications and disabilities caused by RA. The treatment of patients with RA aims to relieve pain and to control inflammation, and the final goal is to achieve remission or at least low disease activity for all patients[9]. The persistent controlling of the disease activity is pivotal in mitigating the detrimental effects caused by it.

An important principle of treating Rheumatoid arthritis is called 'treat to target'which involves frequent assessment of RA disease activity followed by a change in treatment until disease activity is brought down to an acquired target. The goal is to reach complete remission, if that is not possible then the lowest score for disease activity is desired in that particular individual[10].

Materials and Methods

The nature of this research was a prospective observational study conducted in Uttara Adhunik Medical College OPD, Uttara, Dhaka. The duration of this study was one year from January 01, 2019 to December 31, 2019.

A cohort of 55 RA patients enrolled in this study. They were followed for 12 months with follow-up being maintained at 6 months interval for each patient. Data were collected by a checklist, where the particulars of the patient, history of the illness, biochemical investigation profile and clinical evaluation were recorded. The data was collected by skilled data enumerators, blood samples were collected by skilled medical technologist using all aseptic precautions with proper consent from the patient.

All the patients were given standard protocol treatment as per their severity of disease, concomitant co-morbidities and their socio-economic condition. Methotrexate was tried to be kept in the treatment of every patient as an anchor unless it was contraindicated or not tolerated. Other DMARDs (either synthetic or biological) were added as per merit of the case if disease activity was high at the beginning or if there was inadequate control with Methotrexate or with another DMARDs. Even though records were maintained at 6 months interval, patients were seen on a 3 months basis to see if the drugs were causing any side-effects Steroid was also used in some cases to control the aggressiveness of the disease along with NSAIDS or other analgesics depending upon the renal function of the individual.

There are many methods of measuring the disease activity of Rheumatoid Arthritis. The one that was used in this study was DAS 28[11]. The Disease Activity Score uses 28 joint counts (DAS28)[12] and has been widely used in clinical trials and for the assessment of patients in the clinic to monitor disease activity of patients with rheumatoid arthritis.

The DAS28 is calculated from four components: tender joint count, swollen joint count, score of the patients' 'global assessment of health' (indicated by marking a 10 cm line between very good and very bad) and the laboratory parameter of either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)[13,14]. The DAS28 is widely used, and cut-off points of 2.6, 3.2 and 5.1 have been proposed to be indicative of remission, low disease activity and high disease activity, respectively[14].

Data analysis was done with the assistance of Statistical Package for Social Sciences (SPSS)

software. Quality was assured in every steps of the research including protocol development, data collection, data processing, and data entry and analysis.

The clinical evaluation of the patient was based specifically on DAS 28 to evaluate the disease activity and severity of RA patients.

Results

Socio-demographic profile of the patients

The 55 patients enrolled in this study were diagnosed to have RA with 45 of them being women and the rest were men. The data for all 50 patients were available for analysis after 1 year since their enrollment in this study.

The age of the respondents ranged from 21-70 years where the majority of the affected i.e. 30 (54.5%) were from the age group 41- 60 years. 53 (94.6%) of the patients were married and 39 (70.9%) of them being homemakers. Majority of them i.e. 29 (52.7%) resided in rural areas and 11 (20.0%) being illiterate (Table I).

Table I

Socio-demographic profile of the patients (n = 55)

Attributes		Frequency (%)
Sex	Male	10 (18.1)
	Female	45 (81.9)
Age	21-40	15 (27.2)
	41-60	30 (54.5)
	61-70	10 (18.1)
Area of residence	Urban	19 (34.5)
	Semi-urban	7 (12.7)
	Rural	29 (52.7)
Occupation	Homemaker	39 (70.9)
	Service holder	8 (14.5)
	Business	5 (9.09)
	Retired	3 (5.45)
Education	Illiterate	11 (20.0)
	Primary and Secondary Education	25 (45.5)
	SSC and HSC	11 (20.0)
	Graduate and above	8 (14.5)
Marital Status	Unmarried	2 (3.63)
	Married	53 (96.4)

Disease factor and characteristics at baseline

The mean duration of the disease was found to be 6.90 ± 3.38 years with 14 (25.5%) and 9 (16.4%) having co-morbidities and deformities respectively. The mean BMI in this cohort of patients was 24.2 ± 4.45 kg/m^2. Around 13% of the patients presented with extra articular manifestations like anemia, subcutaneous nodules, peripheral neuropathy etc. with 34 (61.8%) of the patients testing positive for RA (Table II). The first joint involvement in the majority of the patients i.e. 14 (25%) were in the interphalangeal joint (Figure -1)

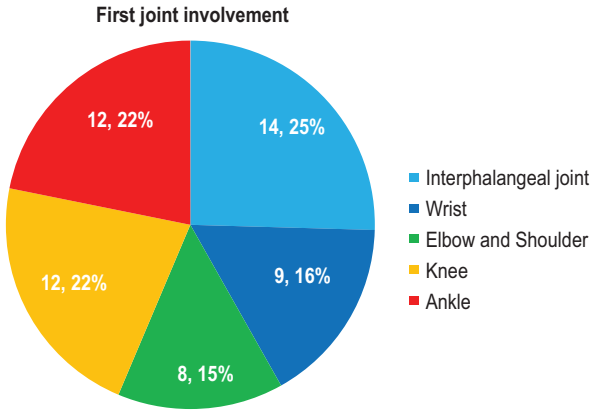

Figure-1: First joint involvement among RA patients

The mean value for the biochemical markers at the baseline was 62.2 ± 29.7 mm/hour and 29.83 ± 5.84 mg/l for ESR and CRP respectively. The mean for Disease Activity Score 28 (DAS 28) was revealed to be 4.69 ± 1.52 where 10 (18.2%) had low disease activity and 18 (32.7%) had high disease activity (Table II).

Table II

Disease factor and characteristics at baseline

Attributes	Value (n = 55)
BMI (kg/m^2), mean ± S. D	24.2 ± 4.45
Disease duration (years), mean ± S.D	6.90 ± 3.38
Tobacco intake, f (%)	12 (21.8)
Co-morbidities, f (%)	14 (25.5)
Deformities, f (%)	9 (16.4)
Extra articular manifestation, f (%)	7 (12.7)
RA test positive, f (%)	34 (61.8)
ESR (mm/hour), mean ± S. D	62.2 ± 29.7
CRP (mg/l), mean ± S. D	29.83 ± 5.84
Hemoglobin (g/dl), mean ± S. D	11.2 ± 1.8
Patient global assessment of pain (mm), mean ± S. D	41.36 ± 20.9
Physician global assessment of pain (mm), mean ± S. D	34.90 ± 20.8
28 swollen joint count, mean ± S. D	3.36 ± 7.56
28 tender joint count, mean ± S. D	9.40 ± 9.84
DAS 28, mean ± S. D	4.69 ± 1.52
DAS 28 <3.2, f (%)	10 (18.2)
DAS 28 >5.1, f (%)	18 (32.7)

Clinical parameters of Rheumatoid Arthritis patients

The comparison of the clinical parameters in the RA patients was done between the baseline and the follow-ups. The data of the follow-ups were recorded at two times, once at 6 months and another at 12 months after the onset of study. The findings unveiled that the DAS 28 score had a gradual decline over the course of 1 year; starting at 4.69 and decreasing to 3.23 (Figure -2).

In addition, the tender and swollen joint counts have also reduced over the progression of 1 year with the count for tender joint decreasing from 7.2 to 2.33 and the count for swollen joint decreasing from 2.71 to 0.15 (Table III).

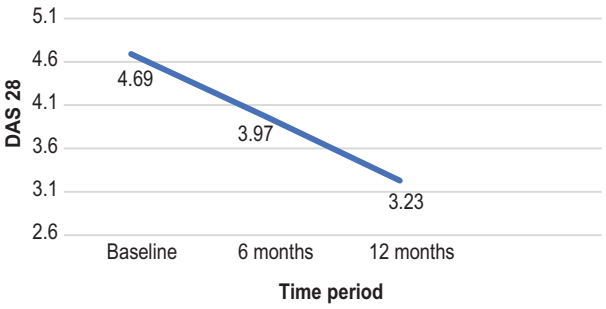

Figure-2: DAS 28 progression over 12 months

Table III

Comparison of clinical parameters of Rheumatoid Arthritis patients between baseline, 6 months and 12 months

Parameters	Baseline	6 months	12 months
Patient global assessment of pain (mm)	41.36	33.36	24.00
Physician global assessment of pain (mm)	34.90	25.90	18.18
Tender joint count	7.2 (3*)	4.76 (2*)	2.33 (0*)
Swollen joint count	2.71 (0*)	0.64 (0*)	0.15 (0*)
DAS 28	4.69	3.97	3.23

*Refers to median value

Discussion

The number of patients affected by this chronic disease was seen to be more in women (81.9%) than in men. This is an expected outcome as the disease worldwide has a higher incidence in women with the onset generally occurs between 30 years and 50 years of age[9].

The disease characteristics during baseline shared some similar findings with studies done in other parts of the world. The biochemical markers of ESR and CRP done in this study had homogenous findings to a study done in Morocco where the ESR was 57.2 mm in 1st hour and CRP was 26.8 g/dl[15]. In addition, the RA test done in this study was found to be positive in 61.8% patient and in Morocco yielded similar result of 62.5%. These findings suggest that the characteristics of RA remain unchanged in spite of different geographical location.

In another study conducted in the United States of America (USA), the duration of the disease was 8.5 years with the majority of the subjects being females i.e. 79.4%[16] which was consistent with the outcome (improvement of DAS 28 score) of this study. However, the difference was noted in the patient's pain assessment. The subjects in the USA complained of being in more pain with a score 64.2 mm in the 100mm scale compared to Bangladeshi patients who scored 41.36 mm. The difference in these two studies can be due to different pain threshold levels of the residents in the two countries.

DAS 28 score in a Spanish study at the baseline was found to be 5.8 ± 0.8 where the most of the respondents i.e. 83.3% had a DAS 28 score greater than 5.1[17]. This was analogous to our study where the DAS 28 score of the respondents on their first OPD visit was 4.69 ± 1.52 and majority i.e. 32.7% had a score indicating high disease activity. The similarity in the two studies can be due to the patients not following proper treatment regimen leading to such raised scores.

The clinical parameters of the RA patients have shown good prognosis where the DAS 28 score declined from 4.69 to 3.23 over the course of one year. In addition, the physician and patients' global assessment of pain has also decreased with marked reduction in the count

of swollen and tender joint. The results were similar to the study done in Africa[15] where similar findings were present along with decrease in duration of morning stiffness and lowering of the biochemical markers. The matching results of the studies done in two different continents were due to the patients following proper treatment protocol and guidelines.

There are some limitations observed in this our study. To begin with, number of patients achieving remission was too smallto form reliable conclusions. Moreover, there was difficulty in obtaining a large sample size for the study due to the COVID-19 pandemic. In addition, there were a considerable number of patients who could not use methotrexate or biologics because of comorbidity or economicreasons.

Conclusion

This study helped in identifying the patient profile and the course of the disease of RA patient in Bangladesh, an Asian developing country. It has also helped to point out the disease prognosis and the difficulties surrounding to obtain proper and complete treatment. The unawareness of consulting with a Rheumatologist and economic problems are the biggest obstacles to treatment in the present circumstance.

The patients enrolled in this study have shown good prognosis which suggests the fact that with proper healthcare policy, it is possible to mitigate the disastrous complications and provide a better quality of life.

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Original Article

Liver Dysfunction in Newborn with Perinatal Asphyxia

Ferdous Ara[1], Nurul Hossain[1], Nayeema Sadia[1], Ishrat Jahan[1], Habiba Anjuman[1], Tahmina Islam[1], Md. Enamul Karim[2]

Abstract

Background: *Perinatal asphyxia contributes greatly to neonatal mortality and morbidity. In developing countries, the need for risk assessment in perinatal asphyxia is obvious because of the high birth rate and limited perinatal resources.*

Objective: *To find out the occurrence of hypoxic hepatitis in full term infant after birth asphyxia as reflected by the rise of aminotransferase.*

Methods: *This was a prospective cross sectional study including 50 neonates admitted at Uttara Adhunik Medical College & Hospital with hypoxic ischemic encephalopathy between January 2014 to June 2014, compared with 25 healthy neonates as control. Liver function was assessed by measuring S.ALT, Prothrombin Time. Hypoxic hepatitis in full term infant after birth asphyxia was reflected by the rise of aminotransferase.*

Results: *Degree of hepatic damage is determined by sarnat and sarnat staging. In group-1 (case) increased S.ALT and prolonged prothrombin time were observed in 36.0% patients. On the other hand, prolonged prothrombin time was observed in 26.0% patients with normal S.ALT in group I patients. More than half (52.0%) patients had stage I, 24.0% stage II and 24.0% stage III. Increased S.ALT and prolonged prothrombin time were observed in 18 patients, out of which 6 (33.3%) patients were in stage II and 12 (66.7%) patients were in stage III. On the other hand, prolonged prothrombin time was observed in 31 patients out of that 13(41.9%) were in stage I, 6(19.4%) in stage II and 12 (38.7%) in stage III, however 13 patient had prolonged prothrombin time with normal ALT, among them all were in stage I. Two (16.7%) babies died in stage III.*

Conclusion*: In babies with perinatal asphyxia, raising of liver enzyme & prolongation of prothrombin time is significant and these impairment directly correlate with severity of perinatal asphyxia.*

Key words: *Liver dysfunction, Perinatal asphyxia.*

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Introduction

WHO has defined perinatal asphyxia as “failure to initiate and sustain breathing at birth”[1]. If lung expansion does not occur in the first minutes after birth, a progressive cycle of hypoxia, hypercapnia and acidosis evolves. During hypoxia, series of protective mechanisms collectively called as ‘diving sea reflex’ attempt to redistribute available blood flow to some vital organs like brain, heart, and adrenals in preference to perfusion of the lungs, liver, kidneys, and intestine[2]. Ultimately it results in serious organ damage and multi-organ failure. Central nervous system dysfunction associated with perinatal asphyxia is referred as Hypoxic ischemic encephalopathy (HIE). HIE is of foremost concern in an asphyxiated neonate because of its potential to cause serious long-term neuromotor sequelae among survivors. Degree of hepatic damage in perinatal asphyxia and hepatic function changes with severity of HIE as determined by Sarnat and Sarnat staging.

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Asphyxia is a combination of both a lack of oxygen (hypoxia) & perfusion (ischemia) to an organ. Perinatal asphyxia (PNA) causes multiple changes in fetuses and newborns. Within minutes of the onset of total hypoxia, a fetus will develop bradycardia, hypotension, decreased cardiac output, and severe metabolic and respiratory acidosis. The initial circulatory response to these changes is increased shunting of blood through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart, and adrenals in preference to perfusion of the lungs, liver, kidneys, and intestine[3]. Although liver involvement is to be expected, it is usually not considered a component of multi-organ failure in PNA[4-5]. Karlo et al.[6] studied the renal function in term newborns with perinatal asphyxia including urinary excretion of â2 microglobulin (â2M).

Objective of this study was to find out the occurrence of hypoxic hepatitis in full term infant after birth asphyxia as reflected by the rise of aminotransferase.

Materials and Methods

This was a Prospective cross sectional study done at the department of Pediatrics at Uttara Adhunik Medical College & Hospital, Dhaka from January 2014 to June 2014. Fifty term asphyxiated infant was admitted in NICU at UAMCH were enrolled as case in the study, after written informed consent obtained from the parents and another 25 healthy term neonates were included as control. Newborn with small for gestational age, sever jaundice, sepsis, congenital anomalies of hepatobilliary system were excluded from the study. In all cases, asphyxia (using APGAR score) and Hypoxic ischemic encephalopathy (HIE) (Sarnat and Sarnat) were included. Because of hypoxemia, different organ systems of the body are affected in perinatal asphyxia. The functional status of liver of the asphyxiated babies was assessed through estimation of liver enzymes to see any correlation existing between enzyme changes and severity of perinatal asphyxia[7]. Degree of hepatic damage is determined by sarnat and sarnat staging.

Data was collected after taking blood sample within 24 hours of birth in control group and from case also & other relevant data by direct observation, follow up and also from the records of follow up of the baby kept in NICU, during hospital stay period at department of Pediatrics in Uttara Adhunik Medical College & Hospital, Dhaka.

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated by frequencies and percentages. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Student t-test was used for continuous variables. ANOVA test was used to analyze the categorical variables, shown with cross tabulation. P values <0.05 was considered as statistically significant.

Results

Table I

Distribution of the studied patients according to investigations done (n=75)

Investigations done	Group I(n=50)		Group II(n=25)		p value
	n	%	n	%	
S.ALT (U/L)					
	15-45	32	64.0	25	100.0
	>45	18	36.0	0	0.0
Mean±SD	40.9	±28.3	27.9	±11.0	0.030[s]
Range (min-max)	15	-92.0	15	-42.0	
Prothrombin time (Sec)					
	10-16 (Normal)	19	38.0	23	92.0
	>16	31	62.0	2	8.0

p value reached from unpaired t-test

Table I shows that 18 (36.0%) patients had abnormal S.ALT (>45 U/L) in group I and not found in group II. The mean S.ALT was 40.9±28.3 U/L in group I and 27.9±11.0 U/L in group II. Nineteen (38.0%) patients in group I had normal prothrombin time (10-16 sec) and 23(92.0%) in group II. The difference was statistically significant (p<0.05) between two groups.

S.ALT (15-45 U/L) patients was found 26 (100.0%) in stage I and 6 (50.0%) in stage II. The mean S.ALT was found 21.0±5.2 U/L in stage I, 42.8±25.5 U/L in stage II and 82.2±6.7 U/L in stage III. Normal prothrombin time (10-16 sec) was found 13 (50.0%) in stage I and 6 (50.0%) in stage II. Prothrombin time was found 17.2±4.7 second in stage I, 20.9±6.8 second in stage II and 20.6±2.7 second in stage III. The difference was statistically significant (p<0.05) among three groups.

Out of 50 babies, two (16.7%) babies died in stage III. The difference was statistically significant (p<0.05) among three groups.

Table II

Association between stage with investigations done (n=50)

Investigations done	Stage I (n=12)		Stage II (n=12)		Stage III (n=26)		p value
	n	%	n	%	n	%	
S.ALT (U/L)							
15-45	26	100.0	6	50.0	0	0.0	
>45	0	0.0	6	50.0	12	100.0	
Mean±SD	21.0	±5.2	42.8	±25.5	82.2	±6.7	0.001[s]
Range (min-max)	15	-32	15	-72	76	-92	
Prothrombin time (Sec)							
10-16 (Normal)	13	50.0	6	50.0	0	0.0	
>16	13	50.0	6	50.0	12	100.0	
Mean±SD	17.2	±4.7	20.9	±6.8	20.6	±2.7	0.047[s]
Range (min-max)	13.1	-30.2	13.2	-30.2	17.6	-25.1	

s= significant

p value reached from ANOVA test

Table III

Outcome according to staging (n=50)

Outcome	Stage I (n=26)		Stage II (n=12)		Stage III (n=12)		p value
	n	%	n	%	n	%	
Alive	26	100.0	12	100.0	10	83.3	0.036[s]
Death	0	0.0	0	0.0	2	16.7	

s= significant

p value reached from chi square test

Discussion

Asphyxia is a combination of both a lack of oxygen (hypoxia) & perfusion (ischemia) to an organ. Perinatal asphyxia (PNA) causes multiple changes in fetuses and newborns. Within minutes of the onset of total hypoxia, a fetus will develop bradycardia, hypotension, decreased cardiac output, and severe metabolic and respiratory acidosis. It is well known that birth asphyxia in newborn infants can cause hepatic hypoxic injury[8-9]. It is a major cause of death and disability among the newborns in less developed countries like Bangladesh[10]. According to WHO between four and nine million newborns develop birth asphyxia each year. Of those, an estimated 1.2 million die and at least the same number develop severe consequences, such as epilepsy, cerebral palsy, and developmental delay[11]. As birth asphyxia in newborn infant can cause hepatic hypoxic injury. The serum activity of ALT is one of the most specific parameter of liver cell injury both in adult and pediatric age group.

In this study 50 term asphyxiated infants were included as study group & 25 term normal infants were included as control group & outcome, particularly mortality correlated with liver dysfunction that is occurred in asphyxiated baby is also observed.

In this study it was observed that 36.0% patients had abnormal S.ALT (>45 U/L) in group I and not found in group II. The mean S.ALT was 40.9±28.3 U/L varied from 15 – 90 U/L in group I and 27.9±11.0 U/L varied from 15 – 42 U/L in group II. Thirty one (62.0% patients in group I had increased prothrombin time (>16 sec) and 8.0% in group II. The mean prothrombin time was 18.9±5.2 sec varied from 13.1– 30.2 sec in group I and 14.1±1.7 sec varied from 11 – 18 sec in group II. The difference was statistically significant ($p<0.05$) between two groups. In addition increased S.ALT as well as elevated prothrombin time was observed in 36.0% patients. On the other hand, prolonged prothrombin time was observed in 26.0% patients with normal S.ALT in group I patients. Godambe et al.[12] mentioned in their study that ALT levels significantly elevated in asphyxiated neonates compared with the controls. Raised ALT was documented in 75% of asphyxiated babies who expired. Similarly, reduced prothrombin index (PI) was noted in a significantly larger proportion of asphyxiated neonates compared to controls. The mean ALT levels in their study were noted to increase from 35.3±28.8 IU/L in mild asphyxia to 65.6±33.2 IU/L in severe asphyxia. Similar results were observed by other workers who noted a rise from 44 ± 61.9 IU/L in mild to 59.5 ± 108 IU/L in severe asphyxia[13-14]. The rise in ALT indicates liver cell dysfunction either due to hepatocyte necrosis or due to changes in the cell permeability. In another study Islam et al.[15] obtained that mean prothrombin time was 15.2±1.8 seconds in study group and 14.8±1.5 seconds in reference group. No significant changes were noted in prothrombin time. Sanchez-Nava et al.[16] showed that ALT was raised among asphyxiated babies, which are comparable with the current study.

In this present study it was observed that more than half (52.0%) patients had stage I, 24.0% stage II and 24.0% stage III. Beken et al.[17] obtained in their study that according to the classification of Sarnat and Sarnat, 30.9% patients had Stage I, 38.3% Stage II, and 30.9% Stage III HIE. Among the 70 asphyxiated patients Islam et al.[15] found 38.6% were in HIE Stage-I, 42.9% in HIE Stage- II and 18.6% in HIE Stage-III. According to the hypoxic-ischemic encephalopathy staging, Martin-Ancel et al.[5] observed that 41.0% infants had stage 1, 21% had stage 2, and 10.0% had stage 3. All the above mentioned studies are comparable with the current study.

In this present study according to stage it was observed that S.ALT (15-45U/L) patients was found normal 100.0% in stage I, 50.0% in stage II and not found in stage III. So ALT in 50.0% patients in stage II was abnormal and 100.0% patients in stage III was abnormal. The mean S.ALT was found 21.0±5.2 U/L in stage I, 42.8±25.5 U/L in stage II and 82.2±6.7 U/L in stage III. Normal prothrombin time (10-16 sec) was found 50.0% in stage I and 50.0% in stage II not found in stage III. So prolonged prothrombin time was found 50.0% in stage I, 50.0% in stage II and 100.0% in stage III. Prothrombin time was found 17.2±4.7 second in stage I, 20.9±6.8 second in stage II and 20.6±2.7 second in stage III. The difference was statistically significant ($p<0.05$) among three groups. Increased ALT as well as prolonged prothrombin time was observed in 18 patients, out of whom 6 (33.3%) patients were in stage II and 12 (66.7%) patients were in stage III. On the other hand, prolonged prothrombin time was observed in 31 patients out of that 13(41.9%) were in stage I, 6(19.4%) in stage II and 12 (38.7%) in stage III, however 13 patient had prolonged prothrombin time with normal ALT, among them all were in stage I. Islam et al.[15] documented that the rise of PT also showed a significant positive correlation with the

severity of asphyxia and the stages of HIE.

Out of 50 babies, two (16.7%) babies died in stage III. The difference was statistically significant ($p<0.05$) among three groups. In another study death rate was found to be 16% in the asphyxiated babies vs. none in the control group[8]. It is consistent with the study of Etuk[18], who found it to be 20.8%. Similar results were also observed in Indian and African studies. Mortality seen in the study of Khatoon[19] in 1989 and Bhuiyan[20] in 1996 was 25.4% and 44% respectively.

Conclusion

This study was undertaken to find out the occurrence of hypoxic hepatitis in full term infant after birth asphyxia as reflected by the rise of aminotransferase and to investigate enzyme pattern in asphyxiated newborn infants. At the end, in prenatal asphyxia enzyme pattern & synthetic function of liver had been altered. So outcome also correlated with prolonged prothrombin time and abnormal ALT.

So this studies suggests that estimation of hepatic enzymes and synthetic function can be useful as a diagnostic tool as well as to detect the severity of perinatal asphyxia and thus early treatment can be provided on the basis of liver function tests.

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Original Article

Knowledge on Family Planning Methods among the Married Women in a Rural Area of Bangladesh

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Abstract:

Background*: Population growth is a threatening condition for developing country like Bangladesh. So, to stay the overcome population explosion we should concern about family planning. As family planning practices help the couples to attain certain objectives so it has been considered an effective way to improve the health of the mother and child and also to decrease the population of the country.*

Objective: *The aim of the study is to observe the knowledge on family planning methods among the rural married women of Bangladesh.*

Materials and Methods: *A cross-sectional study was conducted and data were collected from Gazipur district, Dhaka in November to December 2011. Total 464 married rural women were selected purposively to find the information on various demographic, socioeconomic, and selected programmatic variables including family planning methods and its' uses.*

Results*: The result of the study showed that among the 464 respondents 231 (49.78%) were in age group of 15-25 years. Duration of marital age showed 292 (62.93%) were married for 10 years, most of the respondents 450 (96.98%) had good knowledge on family planning. About 404 (87.07%) respondents used family planning methods . Majority of the respondents 298 (73.76%) were using pills. Maximum opined pill 291(64.67%) as the best method and about half of the respondents (45.79%) started family planning method just after marriage. Most of the respondent's husband had positive attitude (91.6%) towards family planning.*

Conclusion*: This study assessed the behavior of the rural women's on their practice concerning family planning methods. The findings of the study indicated that family planning service was quite satisfactory but still some intervention needed. Regular monitoring and supervision would certainly improve the quality of family planning service in rural area of Bangladesh.*

Key words: *Knowledge, family planning methods, married woman, rural area.*

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Introduction

An expert Committee of the WHO in 1971 defined family planning as "A way of thinking and living that is adopted voluntarily, upon the basis of knowledge, attributes and responsible decision by individuals and couples, in order to promote the health and welfare of the family group and thus contribute effectively to the social development of a country[1].The Government of Bangladesh has decentralized health care facilities more towards the rural community to ensure better access to maternity and family planning services. Community clinic for every six thousand populations and Union Health and Family welfare Centers are well equipped with trained manpower and adequate logistic supplies. Moreover, there are provisions for 3.3 community health workers per 10,000 populations[2]. Uncontrolled population growth is recognized as the single most important impediment to national development. Therefore, the promotion of family planning, especially in countries with high birth rates, has the potential to reduce poverty and hunger, and avert 32% of all maternal deaths and nearly 10% of childhood deaths[3].Bangladesh strides hard to solve ubiquitous problems related to some population issues such as, food shortage, accommodation problem,

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environmental pollution, inadequate health care supply, fertility reduction, reproductive health and reproductive rights of women etc. Family planning program is the mainstay of solving this problem. Considerations as desired family size and child spacing influence contraceptive prevalence among married women at the individual level, while at the macro level, the laws and regulations and cultural norms are important factors that determine access to contraception[4]. Knowledge regarding family planning methods among rural women were knew about family planning. All the women trusted family planning and believed it to be good for their health and 86.6% thought it was good for their children's health[5]. The level of contraceptive use in most developing countries is higher among women in their thirties and typically lowest among teenage women and women in their forties[6]. Ideally, family planning programs should offer a wide range of methods and appropriate counseling, so that users can make an informed choice and easy access to quality follow-up services since these factors are associated with method satisfaction, continuation and switching[7] . Unmet need varies with increasing age and area of residence. Women aged 15-19 had 10% more unmet need than women aged 45-49 (17 and 7%, respectively). Similarly, rural women had a higher unmet need than urban women (13 and 10%, respectively)[8]. Use of family planning methods can contribute to a substantial reduction in fertility and reduce the proportion of unwanted pregnancies as well as maternal deaths that would otherwise occur in the absence of contraception. [9] In 2006, unmet need for family planning was added to the 5th millennium development goal (MDG) as an indicator for tracing process on improving maternal health[10]. Considering the above mentioned facts, Family planning programs should focus on registering 'Target Couple' and segment client to those who belong to lower wealth unities. This approach can taper down the number of couples field worker need to identify for maternity care and family planning services. Moreover, counseling for family planning should begin at the time of providing antenatal care[11].

Materials and method

It was a descriptive type of cross-sectional study to elicit family planning method among 464 married rural women whom were selected purposively residing in East Chandra, Gazipur, Dhaka. Data were collected in November to December 2011. A pre designed questionnaire was developed to use as data collection instrument. The questions were a combination of closed ended and open ended questions. Before the start of the actual study pre testing was done with a prepared questionnaire. After pre testing some changes were made in the questionnaire and then it was finalized for the actual study. Data collected by face to face interview by going door to door in the village. Data processing and analyses were done using SPSS (Statistical Package for Social Sciences) version 17.The results were expressed as proportions.

Ethical Consideration

Before interviewing, a verbal consent were taken from the respondents and they were assured that the collected data would be kept confidential.

Results

Table-I shows that among 464 respondents 231(49.78%) were within the age group of 15-25 years followed by 168 (36.21%) within 25-35 years. Mean age of the respondents was 27 years. Mean marital age was 10 years. 222 (47.85%), 139 (29.96%) of the respondents had secondary level or above and primary level education respectively and 37(7.97%) were illiterate. About (60.35%) of the respondents' husbands were educated up to secondary level or above and(6.47%) were illiterate. Most of the respondents 183 (39.44%) had one children, 137(29.53%) had two children and significant number 73 (15.73%) found without children. Around (73.67%) respondents were housewives and (58.19%) respondents' husbands were survice holder. Table showed that majority (36.21%) respondents' monthly income were within taka 6000-9999 followed by (34.48%) were within taka 10000 or more.

Table-II revealed that majority 96.98% had knowledge on family planning methods. Regarding the source of knowledge most 168(34.49%) perceived knowledge from health centers/ health workers, 165(33.88%) from radio/television. Majority respondents (87.07%) used family planning methods and 60 (12.93%) did not. Among them (73.76%) used oral contraceptive pill followed by (9.90%) used injectable methods. Most of the respondents 185 (45.79%) started using family planning methods just after marriage, 120 (29.70%) after the birth of 1st child. The knowledge on advantages of family planning method use was highest for determining the number of children 271 (51.92%) and the common disadvantage was vertigo 156 (38.61%). Respondents who did not using any methods the main reasons were pressure from husband (31.90%) followed by (18.97%) desired for son. About 221(47.63%) respondents had not any communication with family planning center but (31.90%) communicated with health center occasionally. Majority respondents' husbands (91.6%) were positive about family planning. In the table showed that 451(97.20%) respondents thought their standard of life was improving after adopting family planning.

Table I

Demographic characteristics of the Respondents (n=464)

Variables	Frequency	Percentage
Age in years		
15-25	231	49.78
25-35	168	36.21
35-45	56	12.07
>45	09	1.94
Mean age	27	
Respondents education		
Illiterate	37	7.97
Can sign only	66	14.22
Primary level	139	29.96
Secondary level & above	222	47.85
Respondents Occupatio(n=471)		
House wife	347	73.67
Day laborar	07	1.49
Service holder	103	21.87
Others	14	2.97
Monthly family income		
3000 or less	40	8.62
3000-5999	96	20.69
6000-9999	168	36.21
10000 or more	160	34.48
Husband education		
Illiterate	30	6.47
Can sign only	55	11.85
Primary level	99	21.34
Secondary level & above	280	60.35
Husband occupation		
Day laborer	43	9.27
Business	120	25.86
Unemployed	09	1.94
Service holder	270	58.19
Others	22	4.74
Duration of the marriage		
0-10 years	292	62.93
10-20 years	121	26.07
20-30 years	47	10.13
30 or more	04	0.86
Mean marital age	10	
Number of children		
0	73	15.73
01	183	39.44
02	137	29.53
3-4	64	13.79
5 or more	07	1.51

Table II

Distribution of the respondents by their knowledge about family planning methods (n= 464)

Variables	Frequency	Percent
Knowledge on family planning		
Yes	450	96.98
No	14	3.02
Source to acquire knowledge(n=487)		
Radio/ Television	165	33.88
Health center/ local health worker	168	34.49
From husband	68	13.96
Others	86	17.66
Use of family planning methods		
Yes	404	87.07
No	60	12.93
Usage of methods (n=404)		
Condom	33	8.17
Pill/ Tablet	298	73.76
Inject able	40	9.90
Copper-T	9	2.23
Norplant	7	1.73
Others	17	4.21
Best method (n=450)		
Condom	74	16.44
Pill	291	64.67
inject able	63	14
Others	22	4.9
Starting time of using methods(n=404)		
Just after marriage	185	45.79
One year after marriage	27	6.68
After the birth of 1st child	120	29.70
After the birth of 2nd child	49	12.13
After the birth of 3rd child	23	5.69
Knowledge on advantages (n=522)		92.14
To determine the no. of children	271	51.92
Proper birth spacing	61	11.69
Prevention of unwanted birth	154	29.50
To bring about wanted birth	26	4.98
Others	10	1.91
Knowledge on disadvantages (n-404)		
Bleeding	33	8.17
Lower abdominal pain	53	13.12
Vertigo	156	38.61
Weight gain	95	23.51
Infertility	12	2.97
Do not know	55	13.61
Reasons behind avoiding FP (n=116)		
Pressure from husband	37	31.90
Desire for son	22	18.97
Fear of adverse effects	21	18.10
Religious belief	5	4.31
Others	31	26.73
Attendance in FP center		
Regular	95	20.47
Occasionally	148	31.90
Not at all	221	47.63
Husbands opinion		
Yes	425	91.6
No	39	8.4
Improvement of standard of living		
Yes	451	97.20
No	13	2.80

Discussion

The study on knowledge on family planning among the married women in a rural area of Bangladesh was carried out in East Chandra, Gazipur, Dhaka in which 464 women of reproductive age were chosen by purposive sampling techniques. The aim of the study was to find out the knowledge of rural women about contraceptive methods, their attitude and the state of practice of these methods among them.

Majority of the respondents (49.78%) were within the age group of 15-25 years. Mean age of the respondents was 27 years. So the finding is similar where the median age for the women was 26 years[12]. The educational qualification showed that (7.97%) were illiterate and (47.85%) had secondary education or above. In another study they found 56.93% women were educated up to secondary level[13]. Most of the respondents duration of marriage was within 10 years (62.93%) folllowed by 10-20 years (26.07%) where In another study showed that 47% respondents' were married for 10-19 years[14].Out of 464 respondents, 391(84.27%) families had children while 73(15.73%) had no children. Majority (39.44%) had one children followed by (29.53%) had two children. The trend of family size was more or less similar with another study showed that (85.3%) had children and (14.7%) had no children[15]. In this study most of the respondents (73.67%) were housewives which is less than another study where 94% were housewives[16].

Among the respondents husband's education (6.47%) were illiterate and (21.34%), (60.35%) had primary and secondary or above education respectively. In other study among the married male 36% were illiterate and (28%) had primary education. Maximum about (58.19%) of the respondents husbands were service holder followed by (25.86%), (9.27%) were business man, day laborer correspondingly. In other study the primary occupation of men in rural area 34% was business followed by service holders were 19% which showed dissimilarity with this study[17].

Among 464 respondents (96.98%) had the knowledge about family planning, In BDHS 2007, it was revealed that 99.8% women of reproductive age of Bangladesh knew about family planning methods[18]. The current study showed that majority of participants (34.49%) got information about family planning from health personnel, (33.88%) from media, (13.96%)from husband. Md. Kamruzzaman in his study found that 34.85% and 22.85% respondents got information from health personnel and media in that order[19]. Among different modern and traditional methods, the contraceptives pill ranked first, about (73.76%) of married women were using this method which is more than other study where the rate was 66.0%[20]. Over all (87.07%) of women reported that they were using a family planning method, where the other study found in Nairobi, 75% , 65% in Home Bay and 59% in Matlab were currently using the method of contraception[21]. In present study (64.67%) were familiar with combined oral contraceptive pill followed by (16.44%) were condoms similarly in another study 72.7% were familiar with OCP followed by 76% about condoms[22].

In this study who were not using any methods the commonest cause was pressure from husband (31.90%), others were (18.97%) desire for son, (18.10%) for side effects & (4.30%) for religious belief. Other study identified fear of side effects as major reason for not using contraceptives 46% followed by religious reason 12% and husband pressure 11%[23]. Most of the respondents (45.79%) started using family planning methods just after marriage followed by (29.70%) just after the birth of first child. In another study where contraceptive use rate increases sharply after first child birth[24]. Most of the women thought that advantages of using family planning is to determine the number of children (51.92%) followed by prevention of unwanted child birth (29.50%) and birth spacing (11.69%). Bangladesh and family planning: An overview indicated of the 17% unmet need, 7% is for spacing and 11% limiting births[25]. It was observed that most of the respondents' husband (91.6%) were positive about family planning where in other study almost all the women 98.8% were using a contraceptive method with the knowledge of their husband and had his support for continuing the same[26]. ShabanaAnjum found in the literature review that 78% of husbands approved the use of family planning methods[22]. According to respondents (38.61%, 23.51%,13.12%) opinion the disadvantages like vertigo, weight gain, lower abdominal pain . Thus, 14%, 24% and 16% of current pill, injectable and implant users, respectively, considered that their method caused serious health problems and between 34% and 55% associated the method with unpleasant side effects[21]. 221(47.63%) women had never visited a family planning center. This finding was less than another study where 79.2% had never visited a family planning center[27]. In present study (97.20%) respondents thought that by adoption of family planning they can raise their standard of life.

Conclusion

Bangladesh is one of the most densely populated countries in the world. This population is increasing day by day. This increased population is now one of the major problems in our country. So to solve this problem adoption of family planning methods are very important. This study showed that the knowledge of family planning methods among rural women were satisfactory but further study will help to make more clear view on the use of FP methods in rural area of Bangladesh. Female educational status should be improved to enhance the quality of life, male partner should be aware about complications of large family and motivated to involve in family planning. The easy availability of the contraceptive equipments should be ensuring for the eligible couple. Over all the government should extant more support and facilities to the health and family planning sector to minimize the need of family planning to an acceptable level.

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Original Article

Clinical Profile and Etiological Spectrum of Obstructive Jaundice- An Experience in a Tertiary Care Teaching Hospital of Bangladesh

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Abstract

Background: *Obstructive jaundice is a frequently encountered condition in clinical practice. During the last decade, significant advances have been made in understanding with regards to the diagnosis, staging and efficacy of various surgical and non-surgical management of obstructive jaundice. To diagnose the cause, site of obstruction and management of such a case of obstructive jaundice is indeed a challenging task.*

Objectives: *Obstructive jaundice resulting from obstruction of the biliary tract from a number of benign and malignant etiology. This study was done to evaluate the clinical profile and etiological spectrum of obstructive jaundice in our setting.*

Methods: *In this cross-sectional study, patients with likely diagnosis of obstructive jaundice were evaluated clinically and by necessary laboratory tests.*

Results: *Out of 102 patients, male were 43 (42.2%) and female were 59 (57.8%). Benign obstructive jaundice was 65 (63.73%) and malignant obstructive jaundice was 37 (36.27%). The mean age of patients of benign etiology was 44.63 ± 14.87 years (ranges 18-80 years) while that of malignant etiology was 54.37 ± 11.03 years (ranges 25-75 years). Age distributions in between the two groups were statistically significant (p 0.007). Majority 35 (94.5%) of the patients of malignant etiology were in between 41-75 years of age. In benign jaundice, male were 19 (29.2%) and female were 46 (70.8%) while in malignant jaundice, male were 24 (64.9%) and female were 13 (35.1%). Sex distributions in between the two groups were statistically significant (p 0.001). Moreover, the differences in high bilirubin and alkaline phosphatase levels in between the two groups were also statistically significant (p 0.000). Choledocholithiasis 45 (69.3 %) and periampullary carcinoma 16 (43.2%) were the commonest benign and malignant etiology respectively.*

Conclusion: *Benign jaundice common in female and occurs at a younger age compared to malignant. ERCP and CT-scan play important role in the diagnosis of obstructive jaundice while ERCP have the additional advantage of being therapeutic role as well.*

Key words: *Cholelithiasis, Choledocholithiasis, Cholangiocarcinoma, Obstructive jaundice, Periampullary carcinoma, ERCP (Endoscopic retrograde cholangiopancreatography), MRCP (Magnetic Resonance Cholangio-Pancreatography), CT (Computed tomography).*

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Introduction

Obstructive jaundice (surgical jaundice) in simple terms means the outflow of bile has been obstructed anywhere from the liver to the duodenum[1]. It is caused by a heterogeneous group of diseases that include both benign and malignant etiology[2]. Early evaluation for the precise etiology is of great importance as secondary biliary cirrhosis can occur if obstruction is unrelieved[3]. Moreover, early diagnosis of the cause is very important especially in malignant cases as

curative resection is only possible in this stage.

A correct pre-operative diagnosis is almost possible today because of advances in imaging techniques over the decades[4]. Removal of block relieves the symptoms and often results in cure. In the present day, surgical jaundice has become more of a medical entity as most of the obstructive jaundice cases are managed by Gastroenterologists by ERCP or by stenting rather than by surgeons[5]. There are various causes of obstructive jaundice, but it is most commonly due to choledocholithiasis (also called bile duct stones or gallstones in the bile duct) – presence of a gallstone in the common bile duct[6]. Other causes like, malignancies such as cholangiocarcinoma, periampullary and pancreatic cancers, and benign stricture including chronic pancreatitis have become increasingly prevalent[7-9].

There was also rise in iatrogenic causes of obstructive jaundice, like injury of biliary tract and cholangitis with the increase of invasive procedures performed on the biliary tract[10,11]. Biliary tract disorders can be significantly found in worldwide population, and the quite majority of cases are attributable to choledocholithiasis. 20% of persons older than 65 years in USA have gallstones and around 1 million newly diagnosed cases of choledocholithiasis are reported every year[12]. Patients with obstructive jaundice usually present with complain of yellow skin and eyes, pale stools, dark coloured urine, jaundice, and pruritus[12]. Abdominal pain often misleading for diagnosis– some patients with choledocholithiasis have painless jaundice, whereas some patients with hepatitis have distressing pain in the right upper quadrant. Malignancy often associated with the absence of pain and tenderness during the physical examination[12]. Patients with obstructive jaundice have tendency to develop nutritional deficits, infectious complications, acute renal failure, and impairment of cardiovascular function. Other adverse events such as coagulopathy, hypovolemia, and endotoxemia can be insidious and significantly increase mortality and morbidity[13].

The common etiologies of obstructive jaundice vary from one center to another and from one individual to another[2,14]. However, the management of obstructive jaundice poses diagnostic and therapeutic challenges to general surgeon especially in resource-limited countries. Surgery in jaundiced patient caries a higher risk of post-operative complications compared to surgery in non-jaundiced patient[15]. Determination of the causes of biliary obstruction and assessment of factors that influence the morbidity and mortality in obstructive jaundice will better guide appropriate management and will improve survival. A vast array of invasive and non-invasive tests are available to establish the etiology of obstructive jaundice. An accurate diagnosis can usually be made with combination of different approaches like, history, physical examination, biochemical tests, and when appropriate cholangiography and liver biopsy and observation of the patient's course[16]. Early and precise detection of etiology of obstructive jaundice can help surgeons to accurately manage such patients and thus will improve quality of life of patient and improving the survival rates among the patients with malignant pathology[17]. Very limited studies regarding patients with obstructive jaundice were done in our country. So, this study is being undertaken to describe our own experiences in the management of the patients of obstructive jaundice, outlining the clinical profile, etiological spectrum and investigation findings available in our center.

Materials and methods

This prospective, descriptive study was conducted in the department of Gastroenterology, Uttara Adhunik Medical College Hospital, Uttara, Dhaka, Bangladesh from October, 2015 to March, 2017. One hundred two (102) patients were enrolled in this study. All patients of any age, sex and profession with likely diagnosis of obstructive jaundice were included in the study. All patients with medical jaundice and cirrhosis of liver were excluded from the study. Well-structured questionnaire was made to collect patient's data. A thorough clinical history including the age, sex and relevant features like presence of yellow (high-colored) urine, generalized itching, clay-colored stool, loss of weight, loss of appetite, abdominal pain, vomiting etc. were taken and correlated with the examination findings of presence of jaundice, anemia, scratch marks, hepatomegaly, palpable gall bladder/abdominal mass. A probable diagnosis of obstructive jaundice was made and preceded by the following investigations- Hb%, ESR, bilirubin, alanine aminotransferase (ALT), alkaline phosphatase and prothombin time. Serum lipase level in suspected cases of acute biliary pancreatitis. Abdominal ultrasound was done as initial investigation to look for the abnormality of intra and extra hepatic biliary tree, level and possible cause of biliary obstruction. Followed by CT-scan of upper abdomen for assessment of tumor size and loco-

regional staging in cases of suspected malignant etiology as well as for evaluation of local complications in acute pancreatitis. Magnetic Resonance Cholangio-Pancreatography (MRCP) although a non-invasive test but it was expensive, had only diagnostic role in obstructive jaundice and not available in our center. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in every case for direct visualization of the biliary tree, level of biliary obstruction, clear delineation of the cause, and therapeutic intervention if indicated. Ultimately, final diagnosis was made on the basis of result of advanced radiological investigations (CT-scan, ERCP) and/or histopathology. The results were then compiled.

Results

Out of 102 patients of obstructive jaundice, male were 43 (42.2%) and female were 59 (57.8%). Benign obstructive jaundice was 65 (63.73%) while malignant obstructive jaundice was 37 (36.27%) (figure-I). Mean age of the patients of benign etiology was 44.63 ± 14.87 years (ranges 18-80 years) while that of malignant etiology was 54.37 ± 11.03 years (ranges 25-75 years). Age distributions in between the benign and malignant obstructive jaundice were statistically significant (p 0.007) (table-I). 40 (61.5%) patients of benign etiology were in the age range of 31-60 years while 35 (94.5%) patients of malignant etiology were in the age range of 41-75 years. Among the patients of benign etiology, male were 19 (29.2%) and female were 46 (70.8%) with male: female 1:2.42. Among the patients of malignant etiology, male were 24 (64.9%) and female were 13 (35.1%) with male: female 1.84:1. Sex distributions in between the benign and malignant obstructive jaundice were statistically significant (p 0.001) (table-I). Choledocholithiasis was the commonest benign etiology 45 (69.3 %) while periampullary carcinoma was the commonest malignant etiology 16 (43.2%) (table-II, figure II,III).

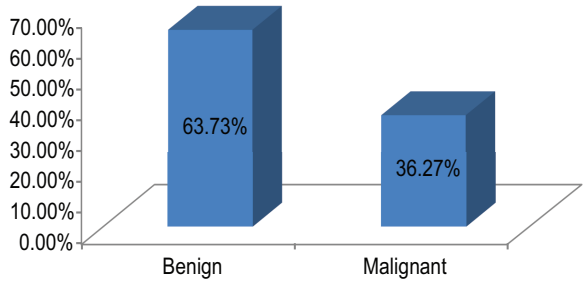

Figure-1: *Benign V/S Malignant causes of obstructive*

Table I

Different factors for benign v/s malignant obstructive jaundice (N-102)

Points	Benign Jaundice	Malignant Jaundice	p value
Age (years)			
≤40	27%	2%	
41-60	26%	23%	0.007
>60	12%	12%	
Sex			
Male	19%	24%	0.001
Female	46%	13%	
Bilirubin(mg/dl)			
≤5	42%	3%	
5.1-10	16%	11%	0.000
>10	7%	23%	
Alkaline phosphatase (U/L)			
≤500	54%	16%	
501-1000	10%	15%	0.000
>1000	1%	6%	

Table II

Different causes of obstructive jaundice (N-102)

Causes	No. of patients (N)	(%)
Benign causes	65	63.73
Choledocholithiasis	45	69.3
Benign biliary stricture	12	18.5
Acute biliary pancreatitis	4	6.1
Post-operative biliary stricture	3	4.6
Round worm in CBD	1	1.5
Malignant causes	37	36.27
Periampulary carcinoma	16	43.2
Carcinoma of gall bladder	11	29.8
Cholangiocarcinoma	8	21.6
Carcinoma of head of the pancreas	2	5.4

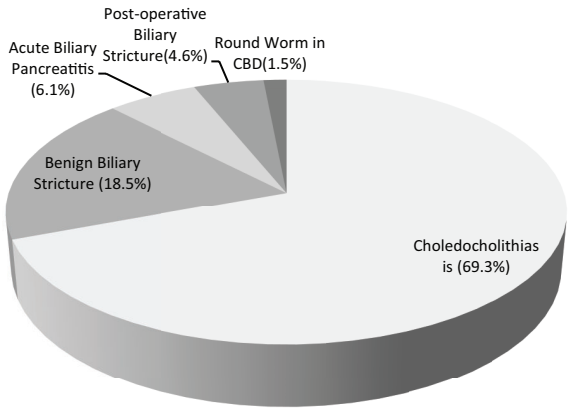

Figure-2: *Benign causes of obstructive jaundice (N-65)*

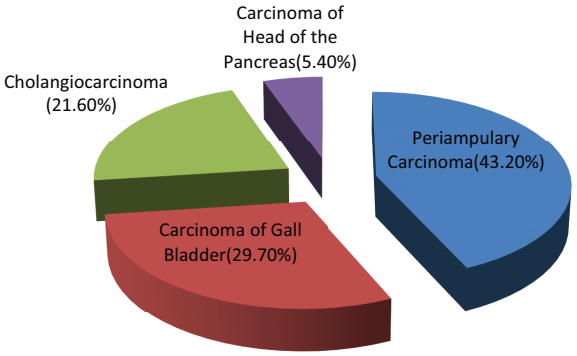

Figure 3: Malignant causes of obstructive jaundice (N-37)

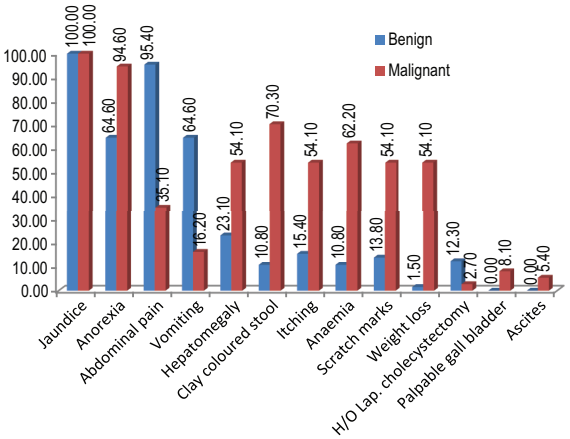

Figure 4: Clinical presentations of obstructive jaundice *(N-102)*

Patients presented with jaundice (100%) associated with loss of appetite (75.5%), abdominal pain (73.5%), vomiting (47.0%), hepatomegaly (34.3%), clay coloured stool (32.3%), generalized itching (29.4%), anemia (29.4%), scratch marks (28.4%), weight loss (20.5%), history of laparoscopic cholecystectomy (8.8%), palpable gall bladder (2.9%) and ascites (1.9%) (figure IV).

Serum ALT level was raised in 88 (86.3%) cases while serum bilirubin and alkaline phosphatase level were raised in all 102 (100%) cases. The means and ranges of different biochemical values shown in table-III. Hb% was lower and ESR was higher in malignant group in comparison to benign group without any statistical significance ($p > 0.05$). The difference in raised serum bilirubin and alkaline phosphatase levels in between the benign and malignant group were statistically significant (p 0.000) (table-I). Serum prothombin time (PT) was raised in all cases but it was much deranged in malignant jaundice.

Ultrasonography (USG) revealed single/multiple findings. Among the patients of benign jaundice, USG showed dilated biliary tree in 39 (60%) cases, stone in dilated CBD in 29 (44.5%) cases, stone in gall bladder in 21 (32.3%) cases, normal biliary tree in 8 (12.3%) cases, acute pancreatitis in 2 (3.0%) cases and round worm in CBD in 1(1.5%) cases. Among the patients of malignant jaundice, USG showed dilated biliary tree in 31 (84%) cases, distended-irregular-thick-walled gall bladder in 11 (29.7%) cases, mass lesion in CBD in 6 (16.2%) cases, ascites in 2 (5.4%) cases and pancreatic mass lesion in 1 (2.7%) cases in malignant jaundice. ERCP was done in every case to find out the etiology of biliary obstruction. Among the patients of benign jaundice, ERCP revealed stone in CBD in 45 (69.3%) cases, benign biliary stricture in 12 (18.5%) cases, acute pancreatitis in 4 (6.1%) cases, post-operative biliary stricture in 3 (4.6%) cases, round worm in CBD in 1 (1.5%) case. Among the patients of malignant jaundice, ERCP findings suggestive of periampullary carcinoma in 16 (43.2%) cases, carcinoma of gall bladder involving the biliary tree in 11 (29.7%) cases, cholangiocarcinoma in 8 (21.6%) cases, carcinoma of head of the pancreas in 2 (5.4%) cases. CT-scan was done in all cases of

Table III

Means and ranges of different biochemical values of study subjects (N-102)

Points	Hb%	ESR	Bilirubin	Alkaline phosphatase	Prothombin time
Benign (N-65)	12.8 ± 1.3	37.8 ± 24.2	6.2 ± 5.3	404.0 ± 177.6	14.04 ± 2.13
	(7.5- 15.9)	(9-112)	(3.1-43.0)	(270-1120)	(12.5-22.0)
Malignant (N-37)	10.8 ± 1.9	73.8 ± 30.9	12.3 ± 5.5	640.7 ± 303.9	17.92 ± 5.19
	(8-14)	(5-130)	(3.4-21.4)	(280-1379)	(12.4-35.0)

suspected malignant biliary obstruction- on the basis of clinical or USG findings. It revealed- periampullary mass in 16 (43.2%) cases, gall bladder mass with dilated biliary tree in 11 (29.7%), mass lesion in CBD in 8 (21.6%) cases, mass in head of the pancreas in 2 (5.4%). Moreover, ascites with multiple gall stone in addition to gall bladder mass found in 1 (2.7%) case and ascites with hilar lymphadenopathy in addition to mass lesion in CBD found in 1 (2.7%) case. Ultimately, final diagnosis was made on the basis of the result of ERCP, CT-scan and histopathology.

Discussion

In this prospective descriptive study, majority (63.73%) cases had benign etiology that was in agreement with other studies[23-25], but most of the study showed malignant etiology was more common than benign etiology[14,18-22]. In our study, benign obstructive jaundice was more common in females while malignant obstructive jaundice was more common in males. Similar observation seen in one study[26] but both the benign and malignant jaundice was more common in female than male in a number of studies[19-20,23].

The mean age of the patients of benign and malignant etiology was 44.6 years and 54.4 years respectively. Malignant jaundice occurred relatively in older age compared to benign jaundice. Similar observation seen in a number of studies[21,27,29].

In our study, choledocholithiasis was the commonest benign etiology supported by other studies[18,20-21,26,31,34]. Periampullary carcinoma was the commonest malignant etiology in our study supported by one study[32] whereas carcinoma of the head of the pancreas was the commonest malignant etiology in a number of studies[18,20-21,26,31,34].

In our study, all the study subjects had jaundice at presentation. Right upper quadrant abdominal pain was the predominant symptom of benign jaundice in our study which was in agreement with other studies[19-21]; but it was found to be more common in malignant jaundice possibly due to locally advanced disease as described in some other studies[18,26]. In addition, loss of appetite, loss of weight and clay colored stool were more common in malignant jaundice than benign jaundice and palpable gall bladder/ abdominal mass seen only in malignant jaundice supporting the 'Courvoisier's law. Similar clinical pattern seen in other studies[19-20,26].

Regarding biochemical investigations- Hb% was lower and ESR, bilirubin, alkaline phosphstase was much higher in malignant group in comparison to benign group. The difference in the levels of raised serum bilirubin and alkaline phosphatase in between the benign and malignant group were statistically significant (p 0.000). Similar biochemical pattern observed in one study[30], but not in agreement with some other studies[19,32]. The values of prothombin time (PT) were raised in all the study subjects but they were much deranged in cases of malignancy. Similar biochemical pattern observed in one study[19].

In our study, ultrasonography (USG) revealed- single/ multiple findings. Among the patients of benign etiology, it showed dilated biliary tree in 60% cases, stone in dilated CBD in 44.5% cases, stone in gall bladder in 32.3% cases, normal biliary tree in 12.3% cases, acute pancreatitis in 3.0% cases and round worm in CBD in 1.5% cases. Among the patients of malignant jaundice, it showed dilated biliary tree in 84% cases, distended-irregular-thick-walled gall bladder in 29.7% cases, mass lesion in distal CBD in 16.2% cases, ascites in 5.4% cases and pancreatic mass lesion in 2.7% cases. On comparison, ultrasonographic findings of one study revealed- dilated CBD in 95% of malignant jaundice and 90% of benign jaundice, distended gall bladder was noted in 60% of malignant jaundice and 30% of benign jaundice, pancreatic mass was noted in 60% of malignant jaundice, ascites was noted in 85% of malignant jaundice[21].

CT-scan clearly delineated any local complication of acute pancreatitis. It was able to pick up the cause and level of biliary obstruction in all cases of malignant jaundice. It has high diagnostic accuracy in cancer detection and loco-regional extension of cancer in malignant jaundice. It is broadly in agreement with other studies[26,33-35].

ERCP was able to pick up the cause, level of biliary obstruction and necessary intervention in every case successfully in both the benign and malignant jaundice. It has high diagnostic accuracy in obstructive jaundice as described in other studies[19,36-38]. It has been described as a 'gold standard' investigation for the diagnosis of obstructive jaundice especially in case of CBD stones[39].

Conclusion

Obstructive jaundice has different etiological spectrum. Benign jaundice is predominant in females while malignant jaundice is predominant in males. Benign causes occur at a comparatively younger age group compared to malignant causes. Along with jaundice, right upper quadrant abdominal pain is the commonest symptom seen in benign group while loss of appetite and clay coloured stool are common symptoms seen in malignant group. Choledocholithiasis was the commonest benign etiology while periampullary carcinoma was the commonest malignant etiology. CT-scan and ERCP are very important diagnostic modalities for obstructive jaundice diagnosis while ERCP have the additional advantage of being therapeutic role as well.

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Original Article

Comparison of Serum Zinc Status in Preeclampsia and Uncomplicated Pregnancy

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Abstract

Background: *Preeclampsia complicates 2-8% of all pregnancies. Preeclampsia is the third common cause of maternal death in the world. In Bangladesh, about 16% of maternal deaths occur due to preeclampsia and eclampsia. One of the potential causes of preeclampsia could be altered trace element metabolism during pregnancy. However, their role in pathogenesis of preeclampsia and their correlation with basic clinical characteristics of such patients is still not clear.*

Objective: *The study was aimed to evaluate the zinc status in pregnant women with preeclampsia.*

Methods: *This case-control study was carried out in the department of Biochemistry, Mymensingh Medical College, Mymensingh, from July 2013 to June 2014. The subjects were selected on the basis of inclusion and exclusion criteria by purposive method. This study included 73 patients with preeclampsia as case Group I (Gr.I) classified into two subgroups according to the gestational age: Gr.I(a); preeclampsia in the second trimester (n = 35), and Gr.I(b); preeclampsia in the third trimester (n = 38). Zinc levels were analyzed and results were compared with 73 apparently healthy pregnant control Group II (Gr.II), and the corresponding gestational age subgroups [Gr.II(a); normal pregnancy of second trimester (n = 35) and Gr.II(b), normal pregnancy of third trimester (n = 38)].*

Results: *The mean serum zinc level was significantly ($p<0.001$) lower in case group than that of control group. Similar extent of reduction was observed in serum zinc level at different gestational age groups of preeclamptic women when compared with corresponding control groups.*

Conclusion: *Estimation of serum zinc level should be incorporated in preeclamptic patients for prevention of complications. Therefore, early detection and supplementation to treat this deficiency may reduce the incidence of preeclampsia.*

Keywords: *Zinc, Uncomplicated pregnancy, Preeclampsia.*

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Introduction

Preeclampsia is a multisystem disorder of unknown etiology associated with increased maternal and fetal morbidity and mortality. Preeclampsia is the third common cause of maternal death in the world[1]. Preeclampsia stands next to hemorrhage and embolism in pregnancy related cause of death. The world Health Organization estimates that globally between 50000 and 75000 women die of this condition each Year[2]. In Bangladesh 16% of maternal deaths are caused by Preeclampsia and eclampsia[3].

Preeclampsia is defined as hypertension associated with proteinuria that arises for the first time after the 20th week of gestation in a previously normotensive woman. Proteinuria resolves completely by the 6th postpartumweek[4]. High blood pressure, swelling of lower extremities, protein in the urine, sudden weight gain, headache and changes in vision are the symptoms of preeclampsia. Increased blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two

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separate readings taken at least four to six hours apart after 20weeks gestation in an individual with previously normal blood pressure is the important sign of preeclampsia[5].

Its etiology remains incompletely understood and many theories have been considered. Normal pregnancy is associated with profound changes in maternal homeostasis. The pathophysiology of preeclampsia is thought to represent a defective response to the physiologic demands of normal pregnancy[6]. Essential trace elements are involved in various biochemical pathways. Their specific and the most important functions are the catalytic role in chemical reactions and in structural function in large molecules such as enzymes and hormones. Alterations in concentrations and homeostasis of each of these micronutrients in body are well-known contributors in pathophysiology of various disorders and diseases such as preeclampsia[7].

Zinc is an important trace element involved in a variety of biochemical functions in the body. Normal homeostasis of zinc is regulated by the actions of zinc transporters like zinc-related protein. These transporters control the level of zinc inside and outside the cell. It has been shown that zinc performs a considerable role for optimal function of more than 300 different enzymes[8]. It is co-factor for the synthesis of number of enzymes, DNA and RNA. Zinc is a structural component of several proteins such as growth factors, cytokines, receptors, enzymes and transcription factors which play an important role in the cellular signaling pathways. Approximately 10% of all protein in human body binds with zinc and the biological activity of these zinc bound protein depends on the concentration of zinc in the body[9].

Zinc acts as an intracellular signaling molecule. Thus, alteration of Zinc homeostasis and dysfunction in the signaling function of Zinc may cause pathogenesis of several diseases. Zinc deficiency has been associated with complications of pregnancy and delivery, as well as with growth retardation and congenital abnormalities in the fetus. Several reports had suggested that zinc deficiency may be associated with increased incidence of preeclampsia[8]. Hypozincemia in the preeclamptic group observed may also result in generation of oxidative stress. It is observed that during pregnancy there is reduction in levels of circulating zinc and as pregnancy progresses further reduction occurs, this may be due to less number of zinc binding proteins and enhanced transfer of zinc from mother to fetus[10].

During pregnancy, zinc is also used to assist the fetus to develop the brain and also to be an aid to the mother in labour. It has been estimated that the total amount of zinc retained during pregnancy is ~100 mg. The requirement of zinc during the third trimester is approximately twice as high as that in nonpregnant women[11]. Plasma zinc concentrations decline as pregnancy progresses possibly due to decrease in zinc binding and increased transfer of zinc from the mother to the fetus. Zinc is passively transferred from mother to fetus across the placenta and there is also decreased zinc binding capacity of maternal blood during pregnancy, which facilitates efficient transfer of zinc from mother to fetus. Zinc is essential for proper growth of fetus and the fall in zinc during pregnancy could also be a physiological response to expanded maternal blood volume[12].

During pregnancy, there is a decline in circulating zinc and this increases as the pregnancy progresses, this might be attributed to decrease in zinc binding and increased transfer of zinc from the mother to the fetus. Zinc deficiency is also related to hemodilution and increased urinary excretion. In pregnant women with preeclampsia, low serum zinc may be partly due to reduced concentrations of zinc-binding protein and estrogen caused by increased lipid peroxidation[7]. This leads us to hypothesize that zinc may play a role in pre-eclampsia through an increase of lipid peroxidation. Recently, the role of oxidative stress or excessive lipid peroxidation has been implicated in the pathogenesis of pre-eclampsia. There is an imbalance between antioxidant enzyme activities and pro-oxidant production. Maternal zinc deficiency is related with serum cortisol level that increases during normal pregnancy and it is much higher in preeclampsia[4].

There are several studies relating to zinc homeostasis in pregnancy. Many of the zinc supplementation studies have been conducted in developing countries where incidence of zinc deficiency is high and benefits of supplementation include reduced incidence of pregnancy-induced hypertension or low birth weights[13]. The study was designed to evaluate the zinc status in pregnant women with preeclampsia.

Materials and methods

The case-control study was carried out from July 2013 to June 2014 in the department of Biochemistry,

Mymensingh Medical College Hospital, Mymensingh. Total 146 subjects were selected by purposive method on the basis of presence of inclusion and exclusion criteria. Out of them 73 clinically diagnosed preeclampsia patient were taken as case, Gr.I and 73 normal Pregnant women were taken as control Gr.II. The exclusion criteria used for both case and control were women having past history of hypertension, pregnancy less than 20 weeks of gestation, acute liver diseases, cardiovascular diseases, diabetes mellitus and systemic and endocrine disorder.

The 73 patients of both case and control were further classified into two subgroups according to the gestational age:

Preeclampsia in the second trimester Gr.I(a): (n=35)

Preeclampsia in the third trimester Gr.I(b): (n=38)

Normal pregnancy in the second trimester Gr.II(a): (n=35)

Normal pregnancy in the third trimester Gr.II(b): (n=38)

Data were recorded by using a pre-designed format of data collection sheet. They were collected after direct interview of patients or attendants. Informed written consent was obtained from direct interview of all patients or attendants. Informed written consent was obtained from all participants. Blood samples were collected and analyzed for investigation. Diabetes Mellitus and liver diseases were excluded by fasting blood sugar and serum ALT respectively, Hypertension and any kind of endocrine disorder were excluded by taking history and clinical examination. Demographic, dietary & medical information and other relevant data were collected and recorded in a preformed data sheet. For laboratory investigations, 5 ml blood were collected, processed and preserved for estimation of different biochemical parameters.

Serum zinc level was determined by colorimetric water soluble pyridylazo dye method[14]. The data were processed and analyzed by computer software SPSS (Statistical Package for Social Science) version 14.0. Student's unpaired t- test was used to analyze the data between groups. Values are expressed as Mean ± SD. For analytical tests, the confidence limit was 95% and $p<0.05$ was taken as level of significance.

Results

Different variables of the subjects were analyzed and compared between case and control. Some physical aspects such as systolic blood pressure, diastolic blood pressure and age were shown in Table I. The study showed that edema was common in preeclampsia patient. Among 73 case, 64 (87.67%) were suffering from edema and 09 (12.33%) were free from edema. In control group edema was completely absent. Out of 73 case, 59 (80.82%) were primigravida and 14 (19.18%) were multigravida mother. Thus primigravida pregnant mother was more prone to preeclampsia than multigravida pregnant mother.

Table I

Characteristics in the study population

Variables	Mean ± SD (case)	Mean ± SD (control)	p value
Age (years)	24.42±2.891	25.04±2.731	p>0.05
DBP (mm of Hg)	100.68±8.552	75.21±5.364	p<0.001
SBP (mm of Hg)	152.47±7.413	118.01±4.620	p<0.001

p<0.001: Highly significant; p>0.05: Not significant
SD - Standard deviation
SBP - Systolic blood pressure
DBP - Diastolic blood pressure

A highly significant reduction in serum zinc level was noticed in preeclampsia group when compared with the control group (p<0.001). It was observed that mean Zinc levels were 80.01±9.038 ìg/dl for case (Gr.I) and 110.15±10.223 ìg/dl for control (Gr.II) group. The similar highly significant reduction in serum zinc level was again observed when case subgroups Gr.I(a) and Gr.I(b) were compared with corresponding control Gr.II(a) and Gr.II(b) respectively (p<0.001). Analysis of mean serum zinc levels of study population were presented in Table II.

Table II

Comparison of mean serum Zinc levels in the study population

Group	Mean ±SD (ìg/dl)	p value
Gr.I	80.01±9.038	p<0.001
Gr.II	110.15±10.223	
Gr.I(a)	87.83±4.712	p<0.001
Gr.II(a)	113.20±10.064	
Gr.I(b)	72.82±5.250	p<0.001
Gr.II(b)	107.34±9.665	

p<0.001: Highly significant; SD - Standard deviation
Gr.I - Case (Preeclampsia patient)
Gr.II - Control (Normal pregnancy)
Gr.I(a) - Preeclampsia in the second trimester
Gr.I(b) - Preeclampsia in the third trimester
Gr.II(a) - Normal pregnancy in the second trimester
Gr.II(b) - Normal pregnancy in the third trimester

It was noticed that serum zinc level was lower in third trimester group as compared to second trimester group. The mean values of serum zinc levels were 87.83±4.712, 72.82±5.250, 113.20±10.064 and 107.34±9.665ìg/dl for the Gr.I(a), Gr.I(b), Gr.II(a) and Gr.II(b) group respectively. The difference in mean serum Zinc levels were highly significant in Gr.I(b) group as compared with Gr.I(a) ($p<0.001$). The levels were observed significantly different if mean serum Zinc levels were compared between Gr.II(a) and Gr.II(b) groups ($p<0.05$). The mean serum magnesium levels were presented in Figure 1.

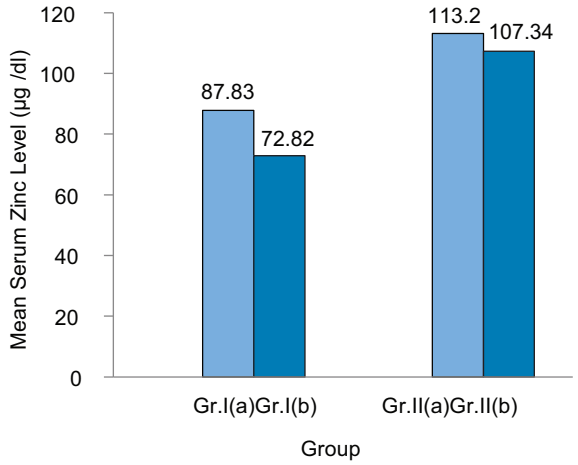

Figure 1: Mean serum zinc levels in the study population according to gestational age
Gr.I(a) - Preeclampsia in the second trimester
Gr.I(b) - Preeclampsia in the third trimester
Gr.II(a) - Normal pregnancy in the second trimester
Gr.II(b) - Normal pregnancy in the third trimester

Discussion

There is no concrete data found on incidence of preeclampsia in our country, but calculated from the US Census Bureau, International Data Base, 2004, the extrapolated annual incidence of preeclampsia in Bangladesh is 76,032.In Bangladesh, the most densely populated country in South East Asia has high maternal mortality as well as fetal mortality rate. According to Bangladesh Demographic and Health Survey 2004, the maternal mortality rate (MMR) is 3.21 per 1000live births and neonatal mortality rate (NMR) is 41 per 1000 live births. There are number of causes for this high maternal mortality rate. Preeclampsia, being one of them, is well known to complicate pregnancy and thus contribute to maternal and fetal death[15].

Preeclampsia and eclampsia are fatal medical complications of pregnancy accounting for 20-80 % of increased maternal death in developing countries. Their etiologies are still under investigation. Serum trace elements have been suggested to be involved in the pathogenesis of preeclampsia[16]. Preeclampsia, a multi factorial disease results on account of generation of oxidative stress in pregnant women. Enhanced production of free radicals and reduced levels of some trace elements necessary for antioxidant defense mechanisms are the important contributors to oxidative stress[7]. Zinc is an important part of antioxidant enzymes required by the antioxidant defense system to protect cells from free radicals injury. It is an integral part of the antioxidant enzyme-superoxide dismutase (SOD). Decreased concentration of zinc in serum, may lead to decrease in activity of this enzyme. Deficiency of these elements may withdraw the effect of antioxidant potential of cells leading to an increase in blood pressure[17].

In this study, serum zinc level was lower in preeclamptic patient than normal pregnant woman. There was highly significant difference in serum zinc level between the case and control ($p<0.001$). Several studies reported that hypozincemia was associated with pregnancy[10,12,13] which support this study. Though, a conflicting result was presented by few studies. They conclude that zinc level was not significantly different between the two groups[1,17]. Again Basima et al. found positive correlation in zinc with preeclampsia[2]. Noura et al. observed that the preeclamptic Saudi women have lower serum level of zinc compared to normal pregnant women[7].

A highly significant reduction in mean serum zinc level was noticed in third trimester when compared with second trimester between the preeclampsia subgroups. Also significant reduction in mean serum zinc level was noticed in third trimester between the two healthy control subgroups. Faisal and Al-Rubaye shows similar result[18]. They found a gradual decrease in mean serum magnesium level with increasing period of gestation in the preeclamptic women. Abdellah et al. observed that there is not enough high-quality evidence to show the relationship between zinc and preeclamptic women[19]. Deepa et al. found a gradual decrease in mean serum magnesium level with increasing period of gestation in the preeclamptic women[13]. This implicates that the level of zinc in preeclampsia was lower than the control group since the beginning of pregnancy.

Several investigators have noted that women with preeclampsia as compared with normotensive pregnant women had lower zinc concentrations. Zinc deficiency in the placental tissue might lead to insufficiency of superoxide dismutase, an antioxidant enzyme. Furthermore, deficiency in placental zinc also plays a role in the biosynthesis of connective tissue, maintaining its integrity, which might have an impact on the structure of the spiral arteries. Several studies have suggested that alterations in maternal serum or plasma zinc levels are found in preeclampsia[4]. Although these findings provide a role of zinc in the development and pathogenesis of preeclampsia, the present study has some limitations: we did not study the dietary intake of preeclamptic women to find out whether the reduced levels of trace elements were from nutritional deficiencies or not. Further study investigating the roles of dietary supplementation of these elements needs to be undertaken.

Different study designs, different techniques of analysis, small samples and different population characteristics such as race, culture, eating habits and geographical regions are possible explanations for the different results of this study with other studies.

Conclusion

In Bangladesh, preeclampsia during pregnancy is increasing day by day[3,10]. However, number of study with similar objectives in Bangladeshi population is very limited. If any correlation between zinc homeostasis and preeclampsia can be verified in Bangladeshi population, this may open up a possibility for effective prevention with zinc supplementation. The present study concluded that preeclampsia was associated with deficiency of serum zinc level. Therefore it may be recommended that routine estimation of zinc level in pregnant women should be carried out for earlier detection and management of preeclampsia. Close monitoring of serum zinc level in antenatal period can reduce the incidence of preeclampsia and also prevent complications of preeclampsia.

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Review Article

Literature Review of Pathophysiology and Management of Pancreatic Neuroendocrine Tumors (PNETs)

Nayeem Al Imam[1], Farzana Yesmin[1], Golam Mehedi[1], Rasel Kabir[1]

Abstract

Pancreatic neuroendocrine tumors (PNETs), a group of endocrine tumors arising in the pancreas, are among the most common neuroendocrine tumors. Both familial and sporadic cause of PNETs does occur but the molecular pathogenesis remains unknown. Pancreatic neuroendocrine tumors (PNETs) are on the increase. Functional tumors including gastrinoma and insulinoma cause well described clinical syndromes. Non-functional Pancreatic neuroendocrine tumors (NF-PNETs) are found incidentally or by direct tumor effects. A third category of tumor secretes hormone(s) at a subclinical level without producing a syndrome. When PNETs may be indolent for several years but progression is inevitable. In this article recent advances in the pathophysiology, diagnosis, and management of these tumors are reviewed and placed in context.

Keywords: *Pancreatic neuroendocrine tumors (PNETs), Insulinoma, Gastrinoma, VIPoma, Glucagonoma, Non-functioning, Multiple endocrine neoplasia syndrome type 1.*

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Introduction

Neuroendocrine tumors are neoplasms that exhibit neuroendocrine phenotypes such as the production of neuropeptides, large dense-core secretory vesicles, and a lack of neural structures[1-3]. Pancreatic neuroendocrine tumors (PNETs), a group of endocrine tumors arising in the pancreas, are among the most common neuroendocrine tumors (NETs)[4]. Functioning PNETs include insulinoma, gastrinoma, VIPoma, glucagonoma, and others that produce specific hormonal hypersecretion syndromes. Non-functioning PNETs comprise the largest group of PNETs and do not produce syndromes of hormonal excess; rather, they cause morbidity and mortality by invading normal tissue and metastasizing[1-3]. There are no clear differences in the epidemiology of PNETs based on race, sex, geographic area, or socioeconomic status[4]. A conservative estimate of the prevalence of PNETs is approximately 25–30 per 100,000 populations in the United States, and the incidence of PNETs is increasing due to improvements in diagnosis and case finding. The behaviors of these tumors are highly variable and range from nearly benign to extremely aggressive, but the majority of PNETs are moderately malignant[1-3]. In this review, we summarize the commonalities of PNET biology, diagnosis, and treatment

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Incidence

The incidence of PNETs is 1 in 100,000 in Asian and European population-based studies. Recently, Halfdanarson et al.[6] reported an annual incidence of 2.2 in 1,000,000, covering a period of 27 years. These data also showed a male gender preference (males, 2.6; females, 1.8) and a higher incidence in PNETs in recent decades[6]. Remarkably, the incidence of PNETs according to autopsy studies is as high as 10%[7]. Furthermore, 19% of all pancreatic lesions incidentally detected by computed tomography (CT) are PNETs[8]. These data suggest a higher incidence of clinically “silent” and benign PNETs than symptomatic and malignant PNETs. Importantly, the incidence of multiple primary malignancies in patients with sporadic PNETs compared with general population is remarkably high. Specifically, malignant gastrinomas and malignant NF-

PNETs are associated with a wide range of other tumors, for example, ovarian, breast, endometrial, bladder, prostate, or esophageal cancer[9]. Although multiple studies address PNET incidence and natural history, definitive data are still lacking because most study designs limit any conclusions that can be drawn as a result of inherent bias. For example, benign PNETs are excluded from national cancer databases, and thus are most likely underrepresented in recent epidemiological studies[10] or studies from large referral centers[11]. This may in part explain the shift in relative incidence from F-PNETs to NF-PNETs in recent years. Whereas in early single-center series, NF-PNETs comprise 18%– 66% of all neuroendocrine tumors of the pancreas[12], recent large, single center or epidemiologic studies classify 68%–90% as NFPNETs[6].

General features of PNETs

There are ten different commonly recognized PNETs which are listed in Table 1. Nine of these is associated with a specific functional syndrome including gastrinomas (Zollinger–Ellison syndrome), insulinomas, glucagonomas, VIPomas (Verner–Morrison syndrome, pancreatic cholera, WDHA

Table I

Established pancreatic neuroendocrine tumor subtypes and syndromes (PNETs) according to frequency of incidence

pNET	Syndrome name	Primary location(s)	Incidence (# new/100,000/yr)	Malignancy (%)	Hormone causing syndrome
A.Functional pNETs					
1.Gastrinoma	Zollinger-Ellison syndrome	Pancreas (30%) Duodenum (60–70%) Other (5–10%)	0.5–1.5	60–90%	Gastrin
2.Insulinoma	Insulinoma	Pancreas (100%)	1–3	5–15%	Insulin
3.VIPoma	Verner-Morrison Pancreatic cholera WDHA	Pancreas 85–95% Other (neural, periganglionic, adrenal)(10%)	0.05–0.2	70–90%	Vasoactive intestinal peptide
4.Glucagonoma	Glucagonoma	Pancreas (100%)	0.01–0.1	60–75%	Glucagon
5.Somatostastinoma	Somatostastinoma	Pancreas (50–60% Duodenal/jejunal (40–50%)	<0.1%. uncommon	40–60%	Somatostatin
6.GRFoma	GRFoma	Pancreas (30%) Lung (54%) Jejunal (75%) Other [adrenal, foregut, retroperitoneal)(13%)	Unknown	30–50%	Growth hormone releasing factor
7.ACTHoma	ACTHoma	4–25% of all ectopic Cushing's syndrome	<0.1%, uncommon	95%	ACTH
8.PET causing carcinoid syndrome	PET causing carcinoid syndrome	Pancreas (100%)(<1% of all carcinoid syndrome)	Uncommon (<50 cases)	60–90%	Serotonin Tachykinins
9.PET causing hypercalcaemia	PTHrPoma	Pancreas (100%)	<0.1%. Uncommon	>85%	PTHrP, other unknown
B.Nonfunctional (NF) PNETs	PPomas NF-PET	Pancreas (100%)	1–3	60–90%	None. Secrete pancreatic polypeptide (PP) (60–85%), chromogranin A but cause no symptoms,

syndrome), GRFomas (growth hormone releasing factor secreting), ACT Homas, somatostatinomas, PNETs causing carcinoid syndrome and PNETs causing hypercalcaemia (PTHrPomas). One PNETs syndrome is not associated with a specific hormonal syndrome and is frequently referred to as a nonfunctional PNETs (NF- PNETs) (also as a PPoma)[13]. None of the latter terms are really correct as NF- PNETs, like other pNETs, in 60–100% secrete various peptides such as CgA, neuron specific enolase, pancreatic polypeptide (50–70%), ghrelin, neurotensin, motilin, or subunits of human chorionic gonadotrophin (alpha or beta subunits) which do not cause any specific clinical syndrome[5,14-16]. In addition to these generally accepted PNETs subtypes, there are a number of other very rare PNETs with functional syndromes in which only a few cases have been reported (Table II). These include PNETs ectopically secreting erythropoietin resulting in erythroblastosis[17]; PNETs secreting renin resulting in hypertension[18]; PNETs secreting GLP-1 or IGF-2 which is associated with hypoglycemia[19,20] and PNETs secreting luteining hormone causing masculinization[21,22]. An enteroglucagon secreting PET has been described mimicking a glucagonoma but also with giant duodenal villi present which resembles features reported with renal/duodenal NETs secreting enteroglucagon as well as a metastatic NET of unknown primary secreting GLP-1, GLP-2 and PYY (Table II)[23-26]. Other hormone-excess states due to over-secretion of gastrointestinal hormones by gastrointestinal tumors have been described including ovarian tumors ectopically secreting PYY resulting in constipation[21,22]; secreting renin or aldosterone causing alteration in blood pressure; secreting serotonin causing the carcinoid syndrome and secreting GLP-1 and somatostatin resulting in diabetes and reactive hypoglycemia. These latter functional tumors are usually not characterized as PNETs although the resemble aspects of PNETs as many are NETs. PNETs frequently ectopically secrete PP (60–85%), neurotensin (30–67%), calcitonin (42%) and in a lesser percentage, ghrelin (5–65%)[14,16,25]. Various studies have proposed that ectopic secretion of these various hormones is also associated with functional clinical syndromes[24,27-33] (Table II). However, most studies support the conclusion that ectopic secretion of any of these four hormones is not associated with a specific clinical syndrome and that they are clinically silent[14,34,35].

Table II

Very rare and other possible functional PNETs syndromes (1–5) cases reported.

PNETs secreting:	Symptoms/signs
A. Very rare PNETs (1–5 cases)	
1. Luteinizing hormone	Altered libido, menstrual abnormalities, hirsutism, infertility[21,22]
2. Renin	Hypertension[18]
3. GLP-1	Hypoglycemic symptoms[19]
4. IGF-2	Hypoglycemic symptoms[20]
5. Erythropoietin	Polycythemia[17]
6. Enteroglucagon	Small intestinal hypertrophy[24],Colonic/ jejunal stasis, malabsorption with or renal/duodenal tumor[25,26] without glucagonoma symptoms/ signs
B. Proposed PNET syndromes	
1. Calcitonin	Diarrhoea[27,28]
2. Neurotensin	Motility, vascular abnormalities[24,29]
3. Pancreatic polypeptide	Watery diarrhoea with or without hypokalemia[29-32]
4. Ghrelin	Effects on appetite, body weight[33]

Pathogenesis

The pathogenesis of PNETs is largely unknown but is growing as a research topic[36,37]. Approximately 10% of all PNETs are components of familial endocrine tumor syndromes such as multiple endocrine neoplasia syndrome type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF-1), and tuberous sclerosis (TSC)[36,37]. The etiology of PNETs within the context of these familial syndromes is the inherited germline loss of the respective tumor suppressor gene. For example, MEN1 is caused by inactivating mutations of the *MEN1* gene. For a more detailed discussion, please refer to the section "Endocrine Tumor Syndromes" of this paper. The exact pathogenetic mechanism that leads to PNET tumorigenesis in these syndromes, however, is unclear. Several studies have been performed on the pathogenesis of sporadic PNETs, which comprise 90% of all PNETs. Loss of chromosome 1, 3p, 6q, 11q, 17p, or 22q and gains of chromosome 4 or 9q have been observed in PNETs[38-42]. It is generally assumed that the loss of a tumor suppressor gene or the gain of an Oncogene is the mechanism by which chromosomal alterations cause PNETs, but stochastic chromosomal number changes are also possible. A few genes that regulate cell proliferation have also been studied. Inhibitors of cell proliferation, including the tumor suppressor genes *pRB* and *p53*, and the cyclin-dependent kinase inhibitor (CKI) $p16^{INK4a}$ are usually intact in well-differentiated PNETs, but p53 abnormalities are common in poorly differentiated PNETs[43-48]. The Oncogene *CCND1* (cyclin D1) is often up-regulated in PNETs, but the ras family oncogenes are not usually detected[45,49]. Recently, an exome study of apparently sporadic PNETs from 68 patients demonstrated that 44% of those tumors harbored mutations in the *MEN1* gene (the same gene, if inactivated, causes MEN1), 43% harbored mutations in two subunits of a transcription/chromatin remodeling complex [death domain-associated protein (DAXX) and thalassemia/mental retardation syndrome X-linked (ATRX)], and 14% harbored mutations in the mammalian target of rapamycin (mTOR) pathway[50].

Just as the cellular origin of PNETs is unknown[51,52], it is unclear whether PNETs arise from precursor lesions[53,54]. Diffuse endocrine cell hyperplasia, dysplasia, and microadenoma are present in the pancreas of patients with MEN1 and VHL and are considered to be precursor lesions[55,56]. The hyperplastic pancreatic endocrine cells in patients with MEN1 and in heterozygous MEN1 mutant mice are polyclonal and retain the normal menin allele, indicating that the deletion of one copy of MEN1 results in pancreatic endocrine cell proliferation without tumorigenesis[55,56]. Loss of heterozygosity (LOH) at the MEN1 locus is present in adenomas as small as 0.3 mm in diameter, demonstrating that these microadenomas are true tumors according to Knudson's two-hit hypothesis of tumor development[57]. Interestingly, the exact pattern of LOH differs between microadenomas, suggesting that these microadenomas arise independently from the hyperplastic background[52,58-60]. Because few clinical adenomas develop but numerous microadenomas are observed, additional mutations must accrue to form larger and clinically significant PNETs. Similar precursor lesions in sporadic PNETs have not been reported. Endocrine hyperplasia, dysplasia, and microadenoma, however, are relatively common incidental pathologic findings in the pancreas; if carefully screened during autopsy, up to 10% of adults harbor these lesions. It is not known whether these lesions are monoclonal. Although most of these lesions are not likely clinically significant, they could represent precursor lesions that give rise to sporadic PNETs because all clinical PNETs have to pass through a microadenoma stage during their growth[60]. It is therefore plausible that PNETs develop from precursor (pre-malignant) lesions, such as hyperplasia and microadenoma, in familial PNET syndromes and in some sporadic cases[60].

Staging and Grading

Although Gastroenteropancreatic neuroendocrine tumor (GEP-NETs) have been a well-recognized entity for decades, the heterogeneity of localization and tumor biology make it a challenge to classify these tumors with optimal prognostic relevance. Whereas the presence of metastases remains the ultimate sign of malignant behavior, clearly a classification system that predicts such malignant behavior based upon histological criteria would be more clinically relevant. The WHO introduced a histological classification system for GEP-NETs (including PNETs) in 2000[61-63]. Based on the work of Capella et al.[64], this system was intended to discriminate benign tumors from low-grade, well-differentiated, malignant tumors. For the WHO classification system, tumor localization, extension, proliferative capacity, and angio-/perineural in vasion must be assessed. This grading system enables discrimination of well-differentiated endocrine

tumor (WDET) with benign and uncertain behavior, well-differentiated endocrine carcinoma (WDEC), and poorly differentiated endocrine carcinoma (PDEC) (Table III). While some authors question the clinical relevance of the WHO histological classification[65], several studies have demonstrated its prognostic value[66–70]. Furthermore, early attempts at correlating WHO classification and DNA microarray analysis results are promising. Duerr et al.[61] were able to show "benign clusters" and "malignant clusters" of PNET gene expression associated with WDET and WDEC, respectively. The tumor–node–metastasis (TNM) staging system for pancreatic adenocarcinoma (American Joint Committee on Cancer, Sixth Edition), when applied to PNETs, also provides survival discrimination by stage for surgical and nonsurgical patients. The demand for standardized oncologic stratification of patients with GEP-NETs led the European Neuroendocrine Tumour Society (ENETS) to propose a TNM staging system for foregut GEP-NETs, including a grading system based solely upon the tumor's proliferative capacity measured by mitotic count and/or Ki-67 index (Table IV)[71]. Recently, the suggested TNM classification was retrospectively validated for 202 foregut NETs. Based upon the survival analysis, the authors, acknowledging limitations concerning the retrospective study design and small cohort, concluded at least equivalence for the TNM staging system compared with previous classification systems[72].

Table III

WHO classification of pancreatic neuroendocrine tumors[63]

1.	Well-differentiated endocrine tumor (WDET)
	• Benign behavior Confined to the pancreas, <2 cm in diameter, ≤2 mitoses per 10 HPF, ≤2% Ki-67–positive cells, no angioinvasion or perineural invasion
	• Uncertain behavior Confined to the pancreas and one or more of the following features: ≥2 cm in diameter, > 2 mitoses per 10 HPF, ≥2% Ki-67–positive cells, angioinvasion, perineural invasion
2.	Well-differentiated endocrine carcinoma (WDEC)
	• Low-grade malignant
	• Gross local invasion and/or metastases
3.	Poorly differentiated endocrine carcinoma (PDEC)

Table IV

Proposal for a TNM classification and disease staging and grading for pancreatic neuroendocrine tumors[71]

TNM		
T	:	primary tumor
TX	-	Primary tumor cannot be assessed
T0	-	No evidence of primary tumor
T1	-	Tumor limited to the pancreas and size < 2 cm
T2	-	Tumor limited to the pancreas and size 2–4 cm
T3	-	Tumor limited to the pancreas and size > 4 cm or invading duodenum or bile duct
T4	-	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)
For any T, add (m) for multiple tumors		

Table IV (Cont'd)

N	**:**	**Regional lymph nodes**
NX	-	Regional lymph nodes cannot be assessed
N0	-	No regional lymph node metastasis
N1	-	Regional lymph node metastasis
M	:	Dstant metastases
MX	-	Distant metastases cannot be assessed
M0	-	No distant metastases
M1	-	Distant metastases

Stage

I	:	T1 - N0 - M0
IIa	:	T2 - N0 - M0
IIb	:	T3 - N0 - M0
IIIa	:	T4 - N0 - M0
IIIb	:	Any T - N1 - M0
IV	:	Any T - Any N - M1

Grade	Mitotic count (10 HPF)	Ki-67 Index (%)a
1	< 2	≤ 2
2	2–20	3–20
3	> 20	> 20

a- Percentage of 2,000 tumor cells. Abbreviations: HPF, high power field; TNM, tumor–node–metastasis

Investigation Diagnostic Work-up:

Figure 1 shows a schematic diagram outlining the clinical work-up for pancreatic NET. Based on the functional activity of the tumor, pancreatic NET can be divided into functional pancreatic NET (F-pancreatic NET) and NF-pancreatic NET. Almost half of pancreatic NETs are functional. Insulinoma is the most common pancreatic NET type; other common types are gastrinoma, glucagonoma and somatostatinoma. F-pancreatic NET can present with a range of clinical symptoms, including Whipple's triad, carcinoid syndrome and watery diarrhea/ hypokalemia/ achlorhydria syndrome[5]. These symptoms, along with specific serum abnormality, allow for early diagnosis. NF-pancreatic NET is more likely to present with symptoms of local compression (obstructive jaundice and back and waist pain) and metastatic lesions.

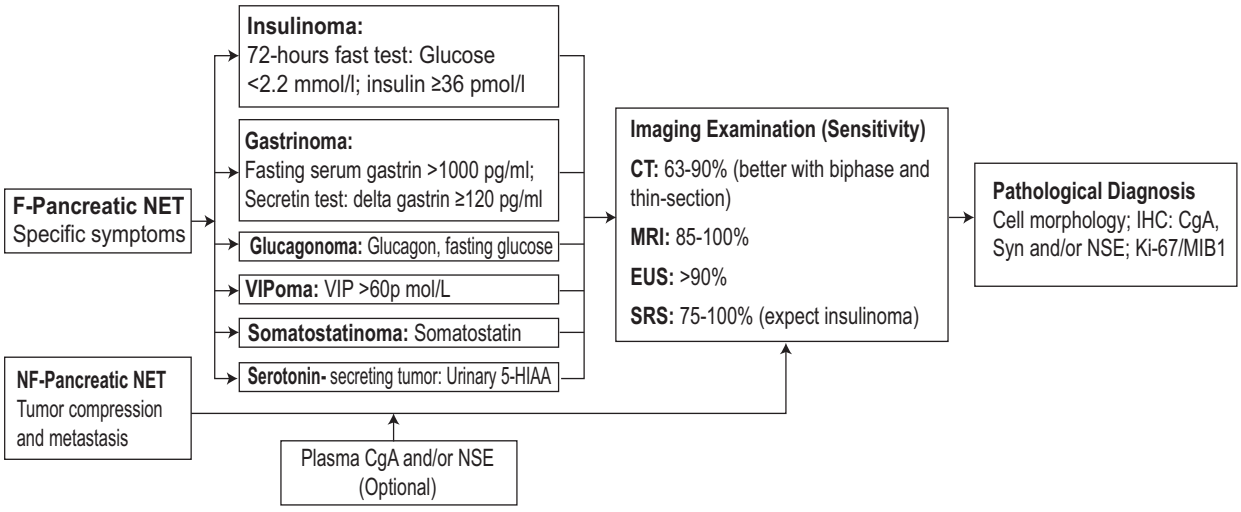

Figure 1: *Clinical work-up of pancreatic NET diagnosis[73].*

Abbreviations: F-pancreatic NET: functional pancreatic NET; VIP: vasoactive intestinal peptide; HIAA: hydroxyindoleacetic acid; CT: computed tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; SRS: somatostatin receptor scintigraphy; IHC: immunohistochemistry; CgA: chromogranin A; Syn: synaptophysin; NSE: neuron-specific enolase; NF-pancreatic NET: nonfunctional pancreatic NET.

Imaging examination

Imaging techniques used for detecting pancreatic NET include computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), somatostatin receptor scintigraphy (SRS) and positron emission tomography (PET)[73-75]. CT/MRI are the most common techniques for the diagnosis of pancreatic NET, especially for NF-pancreatic NET, and have sensitivity and specificity >90%[74]. CT/MRI can also be used for preoperative staging, follow-up and evaluation of treatment efficacy.

EUS is a highly sensitive technique for the localization of small lesions with diameters from 0.3 to 0.5 cm[73]. Although EUS is an invasive procedure, it is widely used because of its high accuracy, safety and probability for pathological diagnosis.

Most pancreatic NET cells express at least two subtypes of somatostatin receptors (SSRs) (Table V). SRS uses radiolabeled somatostatin analogs (SSAs) and can detect tiny primary lesions and distant metastases. Recent results indicate approximately equivalent sensitivity of SRS and CT/MRI for the diagnosis of pancreatic NET[74]. PET may be suitable for the detection of poorly differentiated tumors[76].

Table V

Immunohistochemistry staining of SSTR expression in pancreatic NET[77]

Tumour	SSTR2 (%)	SSTR3 (%)	SSTR5 (%)
Insulinoma	13/21 (61.9)	13/21 (61.9)	9/21 (42.9)
	7/17 (41.2)	Nd	15/17 (88.2)
Gastrinoma	5/5	3/5	4/5
	3/3	Nd	Nd
Glucagonoma	5/5	2/5	3/5
ViPoma	1/1	1/1	1/1
Somatostatinoma	2/4	2/4	2/4
NF-pancreatic	10/13 (76.9)	8/13 (61.5)	8/13 (31.5)
NET	6/6	Nd	Nd

Abbreviations : SSTR : somatostatin receptor; Nd: not done; VIP: vasoactive intestinal peptide; NF: pancreatic NET: nonfunctional pancreatic NET.

Tumor markers

The role of serum tumor markers in diagnosing pancreatic NET is limited. CgA is a member of the chromogranin family and is often elevated in serum of patients with pancreatic NET[78]. The studies showed a moderate diagnostic value of CgA in pancreatic NET[78]. In pancreatic NET, CgA concentration likely correlates with the extent of tumor differentiation, liver metastasis, disease progression and treatment efficiency[79]. NSE has also been evaluated in the diagnosis of pancreatic NET. The specificity of NSE in diagnosing NET is almost 100%, but the sensitivity is low (30–40%)[80].

Role of FNAC

The current results indicated that Ki-67 evaluation in routine EUS-FNA cytology specimens can be used as a potential prognostic marker in pancreatic NETs. Nuclear pleomorphism/multinucleation and the presence of nucleoli also are reliable for predicting malignant pancreatic NETs[81]. EUS-guided FNA is a useful method for the diagnosis of pancreatic NETs. Cytopathologic examination in coordination with immunocytochemistry can provide an accurate diagnosis in most patients[82]. Study showed stronger correlation for Ki-67 values between EUS-FNB and surgical specimens, and that EUS-FNB outperformed EUS-FNA in the evaluation of small PNETs. EUS-FNB should become standard of care for grading assessment of suspected PNETs[83].

Management of PNETs:

The management of these patients has increased in complexity, with better understanding of the heterogeneity of the disease and the increasing number of treatment options. Unfortunately, there is a lack of head to head comparison data. Treatment must be individualized, considering the age and overall health of the patient, the specific toxicities of the potential treatment(s), cost, and potential impact on quality of life. These are decisions that cannot be made in isolation. The importance of an experienced, multidisciplinary team coordinating the management of these patients, together with their primary care physician, cannot be overemphasized.

Nonetheless, there are several general management principles to consider. It is usually helpful to distinguish functional from non-functional tumors, even though this long-standing principle has been questioned[84]. Functioning tumors should be medically controlled to decrease symptoms and morbidity and must be achieved prior to any invasive or surgical procedure, lest there be disastrous consequences for the patient! For a more detailed discussion the reader is referred to various guidelines such as the Vienna Consensus Conference[85].

The grade/ differentiation, and stage/extent of the tumor must be considered. Different treatment schemes are evolving based on these factors. For example, surgical resection is usually advocated for functional, early stage tumors. A wait and see attitude is often appropriate for non-functional, small (<2cm), low grade (G1/G2) early stage tumors, given the indolent nature of most of these tumors.

For patients with metastatic disease, the treatment options are many, and include surgical debulking, systemic therapy including chemotherapy or targeted therapy, liver directed therapy, and peptide receptor radionuclide therapy (PRRT). There are no head-to-head randomized trials comparing the various modalities. Most patients will receive multiple modalities during the course of their disease. There are no data on optimal treatment sequencing. The European SEQTOR trial is examining streptozotocin(STZ)/5-FU followed by everolimus compared to the reverse[86]. There are also few data on relative cost. A U.S modeling study showed a non-significant trend favoring the cost-effectiveness of everolimus compared to sunitinib[87] .

It is not unusual for the management plan to change, based on treatment response and disease progression. Current consensus guidelines do not specifically address the indications for rebiopsy. However, it would seem reasonable to consider rebiopsy (if feasible) when there is a failure to respond to treatment, or an unexpected change in the tempo of disease, as tumor dedifferentiation and tumor heterogeneity are well described in PNETs. The various treatment modalities are discussed below.

Surgical Management

Surgery continues to play a major role in the management of patients with PNETs. Experienced pancreatic surgeons are able resects PNETs with low morbidity and mortality. Indications for surgery include direct tumor related complications such as bleeding, bowel obstruction, or severe pain, to assist in the control of the biochemical syndrome, and in many cases to achieve cure[88].

Surgical resection of a functioning PNET should be considered whenever possible[86,89]. This includes MEN 1 patients with functioning PNETs (other than gastrinoma), as these generally have a high cure rate[90]. Surgery for MEN 1 patients with gastrinoma remains controversial, as they are almost never cured[90-92], and even aggressive resection has not been shown to improve survival[88].

The positive impact of resection on survival in patients with NF-PNETs has been repeatedly demonstrated[93-97]. Small tumors (<2 cm) have an indolent course and may be amenable to observation[98-100]. Factors to be considered in deciding upon surgery include tumor size, tumor grade and differentiation, and overall health of the patient[97,101,102]. Nodal metastases occur in 30% of patients with NF PNETs, are associated with radiological nodal status and tumor grade, and decreased disease-free survival[103]. Thus, some have advocated resection of even small NF PNETs in patients who are otherwise in excellent health.

Indications for surgery in MEN1 patients with NF-PNETs are similar to those with sporadic disease. Patients with MEN 1 and NF-PNETs 2cm or smaller in diameter, who have a low disease specific mortality, may be managed conservatively[104]. Others have suggested resection in MEN1 patients with NF-PNETs more than 1 cm in size and/or demonstrate significant growth over 6-12 months[105].

The traditional surgical approach is open laparotomy. Thorough abdominal exploration including bimanual palpation and intraoperative ultrasound of the pancreas and liver are performed. For small duodenal tumors (especially duodenal gastrinomas) endoscopic trans illumination[118,119] and routine duodenotomy are recommended[91,107].

It appears that certain lesions, particularly those amenable to enucleation or to distal pancreatectomy, may be approached with laparoscopic or robotic techniques, generally with comparable or slightly better results than open resection[88]. Gastrinomas are an exception, as duodenotomy and palpation remain important to detect these often small lesions. Adopting a pure laparoscopic or robotic approach to these tumors will depend upon improvements in haptic feedback technology. For tumors requiring pancreatic head/duodenal resection, laparoscopic and/or robotic pancreaticoduodenectomy (Whipple resection) is being performed at several centers with thus far similar results to open procedures, but at generally increased costs. This technology continues to evolve.

The most common site of distant metastases is the liver, with synchronous metastases noted in about 30%[101,104]. There are multiple options available for the patient with hepatic metastases, including surgical resection which in selected patients appears

to improve survival[108]. Cytoreductive hepatic surgery in patients with functioning PNETs may improve the clinical symptoms by reducing hormone levels and may increase long-term survival[109]. NANETS guidelines suggest that debulking surgery should be considered in carefully selected patients particularly those with functional tumors where the tumors may be removed safely[110]. Surgical debulking may be associated with improved responses to concomitant therapy such as embolization and overall survival[111].

Resection of the primary tumor in the setting of liver metastases remains controversial, given the number of non-surgical options available to treat liver metastases. Both National Comprehensive Cancer Network (NCCN) guidelines[112] and ENETS consensus guidelines[113] recommend hepatic regional therapy with systemic treatment, but do not provide guidelines for managing the primary tumor concurrently. Resection of the primary tumor may prevent some complications which may occur with disease progression[114,115], and may improve survival[116]. An analysis of the SEER database showed a benefit to resecting the primary tumor in all disease stages, including stage 4. Important considerations include the extent of resection required for the primary, the extent of the liver metastases and their planned treatment, as well as the age and overall health of the patient. Aggressive surgical resection of both primary and metastatic lesions has been reported in selected patients with good results[99,109], even when the primary is locally advanced requiring vascular resection.

To summarize, multiple surgical controversies persist including the role of surgery in patients with MEN1 and gastrinoma (we would argue few or none, except perhaps for lesions>3cm), the extent of the surgical resection, the role and extent of lymphadenectomy, the role of resection of the primary in patients with metastatic disease, and the role of surgical debulking when complete resection cannot be achieved. For further details the reader is referred elsewhere[88].

Follow-up

Although evidence for reasonable follow-up or control of treatment efficacy is poor, we suggest a follow-up scheme closely related to the ENETS recommendations[117] and geared to WHO histological grading (Table V)

Table V
Recommendations for PNET follow-up

Tumor	Interval	Investigations
Benign WDET	Every 12 mos	CgA serum levels; if applicable, hormone levels Imaging studies(ultrasound)
Uncertain WDET	After 6 mos	SRS (in case of SRS-positive primary, once-only investigation)
	Every 12 mos	CgA; if applicable, hormone levels Imaging studies (ultrasound CT, MRI)
WDEC–M0	Every 6 mos	CgA, NSE Imaging studies (ultrasound, CT, MRI, SRS)
WDEC–M1, PDEC	Every 3 mos	CgA, NSE Imaging studies (ultrasound, CT, MRI)

Abbreviations: CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging; NSE, neuronspecific enolase; PDEC, poorly differentiated endocrine carcinoma; SRS, somatostatin receptor scintigraphy; WDEC, welldifferentiated endocrine carcinoma; WDET, well-differentiated endocrine tumor.

Prognosis

Nonetheless, the factors associated with long-term survival after resection of PNETs remain controversial. Bilimoria et al.[118] recently conducted a multivariate analysis of long-term survival on the largest cohort of patients (n = 3,851) after PNET resection reported to date. Identified factors adversely affecting survival were age (>55 years), NFPNET, poor tumor differentiation, distant metastases, and surgical procedure (pancreaticoduodenectomy). A prognostic score that incorporated age, histological grading, and the presence or absence of distant metastases significantly predicted long-term survival outcome. That study[118] could not reproduce tumor size or nodal status as independent predictors of poor long-term survival outcome, as reported by earlier smaller multivariate analyses[66,119]. Because the U.S. national cancer database captures only malignant PNETs, this result might be biased by the selection of larger tumors (81% of analyzed tumors were >2 cm). Because prospective validation of either the WHO classification or TNM classification is still not available, clinical implementation of a standardized classification system is incomplete. Thus, comparability of classification data remains a fundamental obstacle to further investigation of the disease[120]. Numerous retrospective reports on the prognosis of PNET patients have been published. The marked heterogeneity among the patient populations as well as the large potential for referral bias, however, reduce the generalizability of the results. After surgical therapy, patients with insulinomas generally have an excellent long-term survival outcome. Cure was achieved in 98% of patients after surgical resection in a large patient cohort from the Mayo Clinic in Rochester[121,122]. The 5- and 10-year disease-specific survival rates of all patients with sporadic gastrinoma were reported at 100% and 95%, respectively, and 40% of the patients were reported to be free from disease at 5 years postoperatively[123]. In the case of NF-PNETs, 5-year overall survival rates are in the range of 26%–58%. After adjustment for age, similar survival data were obtained for sporadic and MEN-1–associated PNETs.

Conclusion

Management is often limited by different aspects of the disease, for example, its relative rarity, the limited understanding of tumor biology and behavior, heterogeneous clinical presentation, and the lack of prospectively evaluated risk stratification systems, and thus, incomplete implementation of staging systems. Thus, prospective tumor registries and tissue banks are required to scrutinize the value of different classification systems and search for biomarkers of PNETs biology, possibly resulting in new diagnostic and therapeutic strategies and thus better outcome of the patients contribute.

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Case Report

Renal Lymphangioma : A Case Report

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Abstract

Renal lymphangioma is an uncommon disorder of the kidney characterized by developmental malformation of the renal lymphatic system[1].It may occur in both children and adults and could be unilateral or bilateral.

In the present study, we report a case of woman aged 28 presented with fever and chills associated with abdominal pain for 3 days.After thorough evaluation by history, physical examination, radiological imaging, and histopathology, renal lymphangioma was diagnosed in the lower pole of the left kidney.

Renal lymphangioma could be asymptomatic or may present with a variety of acute, intermittent or chronic symptoms. Although computed tomography scan is useful in confirming the structural abnormality, final diagnosis requires histopathological analysis.

***Key words**: Renal lymphangioma, Lymphangiectasia.*

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Introduction

Renal lymphangioma is a rare hamartoma in which lymphatic tissue of the kidney fails to communicate with the rest of the lymphatic system[1,2]. The course of the disease varies. It has been reported to appear as multilocular cystic mass on ultrasonography, computed tomography or magnetic resonance imaging. Different treatment options have been proposed, ranging from symptomatic management to percutaneous or laparoscopic drainage and nephrectomy in the most severe cases.

Case

A 28-year old gentle lady presented with the complaints of fever for 3 days with abdominal pain, mostly on Left lumber region. She had intermittent fever associated with chills. In addition, she had urinary frequency but denied any other urinary complaints like urgency, dysuria, and hematuria. Abdominal pain was dull with no radiation associated with feeling of heaviness. Bowel movement was normal. The patient had no significant medical history except gestational hypertension and caesarian section 11/2 year back due to preeclampsia.No previous history of urinary tract infection or stone disease. No significant family history was noted. Physical examination revealed temperature 101*F, pulse 96 beats/minute, blood pressure was 120/75 mm of Hg. On abdominal examination, there was mild tenderness over left lumber region. Other systems revealed no abnormality.

Regarding investigations, complete blood count and urinalysis werenormal. Biochemical investigations revealed normal renal and liver function. Chest X-Ray was within normal limit.

Ultrasonography of the abdomen (Figure 1) revealed left kidney is enlarged in size with well-defined cortex and medulla. One thick walled, multi-loculated, thick septated cystic mass measured about 67x64 mm in size is seen in anterior aspect of lower part of Lt kidney.

CT scan of the abdomen (Figure 2 & 3))with contrast revealed large complex cystic mass, 7.09 cm X 6.8 cm X 6.87 diameters, is noted atanterior aspect of interpolar region of left kidney (Bosniak type IV). Thick internal septation and peripheral solid components are seen within the lesion which shows enhancement on post contrast images.

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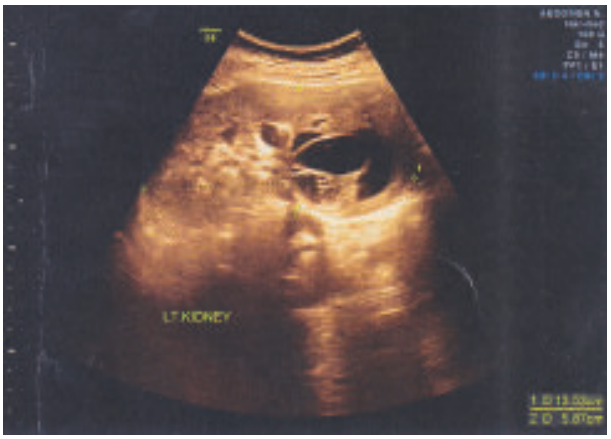

Figure 1: Ultrasound of left kidney

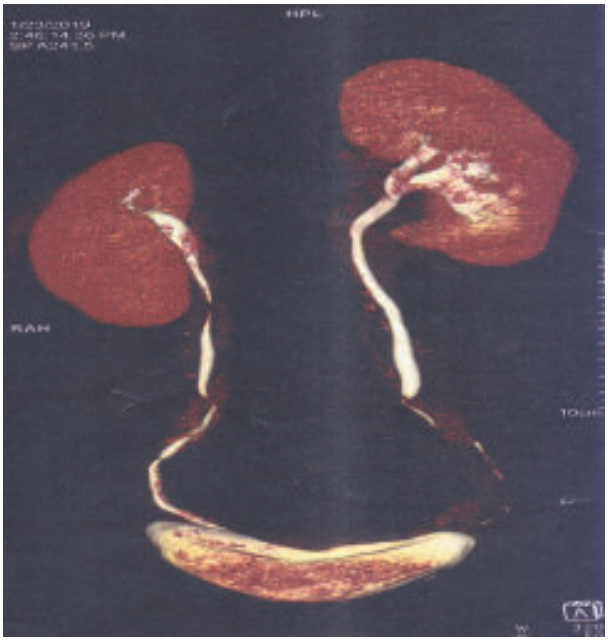

Figure 2: CT Urogram

Patient was treated symptomatically initially and was sent to urologist for further evaluation. Considering the size, symptoms and CT findings, patient was discussed about the surgical options with possible outcome. Left radical nephrectomy was done and post-operative period was uneventful and specimen was sent for histopathological examination.

Histopathological examination showed renal parenchyma with a lesion composed of multiple cystic spaces lined by flattened endothelial cells. Small clusters of lymphocytes with few plasma cells are seen. No evidence of malignancy and no parenchymal abnormalities are noted. Dilated lymphatics are seen. Features suggestive of multiloculated cystic lesion, consistent with Lympahngioma of left kidney.

Figure 3: CT Urography

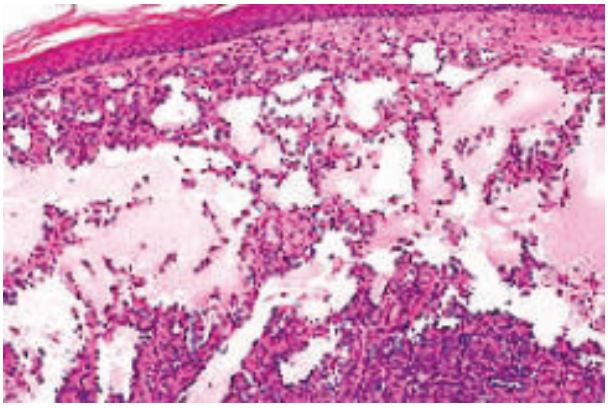

Figure 4 : Histopathology of renal lymphangioma

Discussion

Lympahngioma is a hamartoma of the lymphatic system in which lymphatic tissue fails to establish communication with the remaining lymphatic system leads to distal dilatation of the lymphatic system[2]. It is mostly seen in neck and axilla (95%), also in the retro peritoneum, mediastinum, mesentery, colon, and rarely in the perirenal space[3]. Renal lymphangioma is also known as cystic lymphangiomaif large cystic malformation, renallymphangiectasia, renal sinus polycystic disease and renal hygroma[4]. These tumors may present at any age from childhood to geriatric group with more predilection to female (60%). The exact cause is unknown but is it thought due to congenital malformation. It could be associated with

a positive family history[5]. Some studies show association with certain genetic mutation, such as deletion of Monosomy X chromosome, Trisomoy 7q, mutation in the VHL (Von Hippel-Lindau) gene, Wilms tumor of the kidney in children[6].

The presentation of renal lymphangioma can vary from individual to another. It could be asymptomatic and can be diagnosed incidentally on radiological imaging[7]. Patients may present with flank pain, abdominal pain, urinary frequency, hematuria, fatigue, weight loss[8]. Patient may present with complication like renin dependent hypertension, frequent infection of the urinary tract system, deterioration of renal function.

Renal lymphangioma must be evaluated from other differentials like autosomal-dominant polycystic kidney disease (ADPKD), hydronephrosis, cystic renal dysplasia, renal cell carcinoma, mesoblastic nephroma[9].

After thorough medical history and meticulous physical examination, following tests can be considered:

- Ultrasound scan of the abdomen
- Plain X-ray KUB
- CT scan/MR|I of the abdomen with contrast
- Urinalysis Renal function test

After the initial diagnosis with the above modalities, a tissue biopsy of the tumor is needed to make a definitive diagnosis.

Treatment depends vary due to tumor size, symptoms and signs of the patient. If tumor size is small and asymptomatic or diagnosed incidentally, usually patient is kept in regular follow up. Typically, a surgical excision of lymphangioma of kidney with its entire removal is the treatment of the choice. The methods of surgery may be laparoscopic aspiration, marsupialization of the cyst, nephron sparing surgery, partial or complete nephrectomy. Sclerotherapy may be considered in unilocular lesion& bilateral lesion[10].

In most cases, the prognosis is excellent as it is a benign tumor, especially for small-sized solitary tumor is excellent with surgical intervention. As there is no established preventing measures for lymphangioma, regular medical evaluation and screening through ultrasound at periodic intervals are recommended for who has family history of renal lymphangioma.

Conclusion

Renal lympahngioma is exceedingly rare disorder of the kidney due to lymphatic obstruction. It is a diagnostic challenge as it is infrequent and may remain asymptomatic. Surgery with total resection is the favorite treatment but no treatment is required in small lesion without any symptoms and needs regular follow-up.

Ethical consideration

Written informed consent was obtained from the patient for publication of the case report and related images.

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Case Report

Can a Baby Grow till Term within Just Half of the Uterus? A Case Report

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Abstract

Septate uterus seems to be strongly associated with an adverse pregnancy outcome. A 20 Years old lady presented with a history of previous abortion at 2nd trimester and severe dysmenorrhea. Second pregnancy was by ovulation inducing drugs. At 7 weeks of pregnancy, USG detected septate uterus. She was treated as a high risk case throughout the pregnancy. During surgery at 37 weeks thick complete uterine septum was detected. A healthy female baby was delivered with good postoperative outcome. Successful implantation and fetal development might occur without prior metroplasty, as described in our case report.

Key words: *Septate uterus, Congenital uterine anomalies, Pregnancy outcome.*

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Introduction

Incomplete resorption of the mullerian duct during embryogenesis leads to mullerian anomalies which may alter the reproductive outcome of the patients. The mean incidence of uterine defects in the general population 1 to 3%[1] and in infertile women is 4.3%[2]. In patients with recurrent pregnancy loss, the incidence of uterine defects increases by 5-25%[3,4]. Mullerian duct anomalies represent a group of congenital malformations that result from failure to complete bilateral paramesonephric duct elongation, fusion, canalization, or septal resorption. These anomalies can be classified according to the American Society of Reproductive Medicine (ASRM) as segmental mullerian hypoplasia or agenesis (Group I), unicornuate uterus (Group II), uterine didelphys (Group III), bicornuate uterus (Group IV), septate uterus (Group V), arcuate uterus (Group VI), and diethylstilbestrol related anomalies (Group VII)[5]. Septate uterus (class V) is the most common congenital uterine anomaly, comprising approximately 55% of mullerian duct anomalies. Often a septate uterus doesn't cause any symptoms until puberty when it may cause menstrual pain that is greater than normal[6]. A septate uterus is not a primary factor for infertility[7]. Nearly 40% of patients with septate uterus have reproductive failure, an increased incidence of recurrent miscarriages and obstetrical complications like premature labor, breech presentation, caesarean delivery, postpartum hemorrhage[8]. Clinically, symptoms may range from being asymptomatic thus remaining undiagnosed, to the development of poor reproductive outcome[9].

A septate uterus cannot be diagnosed on bimanual examination but may be recognized by passing a sound, as may the more extreme malformations[10]. More recently, the use of transvaginal 3D ultrasound has proved to be extremely accurate in the detection and classification of uterine anomalies[11]. The diagnosis is best made by hysteroscopy or hystero-salpingography. MRI is an excellent modality for accurate diagnosis, but is more expensive[11].

The treatment of septate uterus depends on the exact state of affairs present and on the symptoms produced. Many are best left untreated. When a septate uterus has caused not less than three miscarriages and no

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pregnancy has resulted in a viable child, surgery may be indicated. With the advent of operative hysteroscopy, the operation for septate uterus has been remarkably simplified. The septum is cut hysteroscopically by sciossors.

In this case we reported a successful pregnancy in one half of uterine cavity with history of previous abortion at 2nd trimester. Finally, the women gave birth to a healthy baby in our hospital.

Case

Mrs. XX, 20 yrs old, para 0+1, presented with a H/O 1 mid-trimester abortion 3 months back. In addition, she had a history of severe dysmenorrheal for 7 year.

Her menarche was at 13 yrs. with regular painful cycles that lasted 7 days. She is married for 3 yrs. She was not on any contraceptive method. She had a history of miscarriage at 6 months pregnancy 3 months back. She was treated with Mefenamic acid 500mg thrice a day for the dysmenorrhoea. 1 year later she came with the complaints of failure to conceive for last 6 months, for which she was treated with Letrozole 5mg daily (from day 3 to day 7) with day 12 TVS finding one dominant follicle (21×21)mm with endometrial thickness 8.3mm. Her pregnancy was confirmed in the next month by USG (reporting septate uterus with 7 weeks pregnancy in one sided cavity). Her LMP was on 19/05/2019 and EDD was calculated as 26/02/2020. As she has previous bad obstetrical history. She was treated with tab. Allylestrenol 5mg thrice a day and Inj. 17á-hydroxyprogesterone twice weekly I/M along with iron, calcium throughout pregnancy. During her follow up schedule, she was admitted twice, 1st at 12 weeks due to hyperemesis and subsequently at 20 weeks due to threatened abortion.

She was subsequently followed up at the antenatal clinic and had no concern till 37 weeks when she presented with a H/O less fetal movement (2-3 times/day) for 2 days. So, she was advised to admit in the obstetrics and gynecology department.

On admission her pulse was 90 bpm, blood pressure recorded to be 100/70 mmHg. On obstetric examination: uterus was deviated to right side, SFH was 36cm, there was a single baby with longitudinal lie, cephalic presentation, head was not engaged, FHS was recorded to be 140/min.

Early USG reported septate uterus with 7 weeks pregnancy in one sided cavity.

She had a normal CTG and obstetric ultrasound (reporting a single live pregnancy of 36 weeks with cephalic presentation). With left lateral position and O2 inhalation, still she perceived less fetal movements for a day. So decision for LUCS was taken on the following day. She underwent cesarean delivery at 37 weeks.

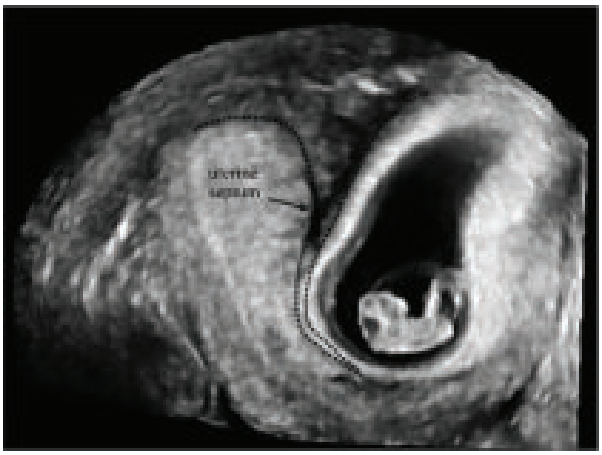
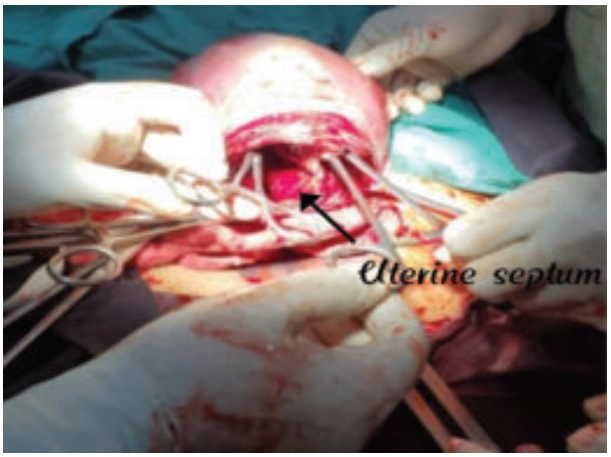


Figure 1: Septate uterus in early pregnancy (7 weeks). The dotted line demarcates the uterine septum. A viable pregnancy is located at the right side of the septum.

The outcome was a live female baby with birth weight of 2.8 Kg, and APGAR of 8 at 1 min and 10 at 5 min.

During C/S a thick septum was found in the uterine cavity with single cervical canal, and fetus was present in the right side of the septate uterus. Uterus was closed very carefully and meticulously by keeping the cavity patent with the cervix.



The arrow mark showing thick uterine septum

Her post operatively per vaginal bleeding was average and had unremarkable post-operative recovery. She was discharged on the 5th post-operative day.

Discussion

Uterine anomalies are related to an increased risk of infertility, miscarriage, premature birth, fetal loss and cesarean delivery[12,13]. In present case, according to the patient history, septate uterus has influenced her fertility and there was a previous history of 2nd trimester abortion. Other than a miscarriage there was severe dysmenorrhea which is also a symptom of a septate uterus. It's often only diagnosed after an investigation into the cause of miscarriages.

Most of the uterine septi are diagnosed by fertility subspecialists, after the patient presents with pregnancy loss. It is important that fertility specialists make the correct diagnosis of the uterine septum versus a bicornuate uterus. The uterine septum contains a separation in the uterine cavity, however the outer appearance of the uterus is normal. A bicornuate uterus at the other hand has a completely separated upper end both internally and externally. Diagnosing this properly is very important since an attempted resection of the bicornuate uterus that is improperly diagnosed as a uterine septum might create a uterine perforation.

Ultrasonography is a simple, quick, and non invasive technique for detecting and diagnosing uterine anomalies. With the notable advantages of this technique, the obstetric ultrasound scan done on our patient in her first pregnancy could detect the septate uterus as anomalies accordance with uterus exactly. However, MRI images diagnosed this problem accuracy.

Hysteroscopy remains the standard for evaluation of intracavitary abnormalities. Its use is especially practical, as it offers the opportunity for treatment at the time of diagnosis. The septum incision is performed with a hysteroscopicresectoscope and it may be controlled under laparoscopic supervisión.

Although hysteroscopy is now the preferred method for treatment of the septate uterus, two case reports described successful removal of the septum at the time of cesarean section. The difficulty in achieving complete uterine septum caesarean has been reported[14,15], however in the present case we didn't found any trouble. As the septum was very thick it was not removed at the time of cesarean section because torrential haemorrhagemight occur. Uterus was closed very carefully and meticulously by keeping the cavity patent with the cervix.

Conclusion

The reported prevalence of the septate uterus in different populations, including women with normal fertility, infertility, and repeated pregnancy loss, varies widely, partly because the methods used for diagnosis differ between investigators.

Early diagnosis and proper antenatal care is required to successfully manage a pregnancy with septate uterus. Patient with mullerian duct anamolies are known to have a higher incidence of infertility, repeated first, second trimester spontaneous abortions intrauterine growth retardation, fetal malpositions, preterm labor, prelabour preterm rupture of membranes & retained placenta. Anticipation and preparedness to deal with these known complications will ensure positive outcome for the mother and baby.

The finding of a septate uterus perse is not an indication for surgical intervention because it is not always associated with poor obstetric performance. However, when a septate uterus is found in association with adverse reproductive outcome, surgical intervention ought to be considered[15].

In conclusion, the diagnosis of septate uterus as a congenital anomaly can be achieved by 3D USG and MRI. It can be corrected by hysteroscopic surgery if needed and thereby decreases the rate of abortion for women greatly.

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