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Editor's choice

This is a great pleasure for us that we are going to publish "The Beacon Medical Journal" first issue in January 2018. Next issue will be published in July 2018. The journal will publish 2 issues/year as regular basis. Ten thousands copy/issue will be distributed to graduate doctors throughout the country by our field colleagues. Already we had form a strong advisory and review board to attract the attention of its authors and readers nationally and internationally. Editorial of this issue is 'chikungunya fever during pregnancy'(P-01). At present chikungunya fever is a burning issue in Bangladesh. Exposure to chikungunya in pregnancy has an increase risk of miscarriage or other congenital malformation. Here symptoms of chikungunya, diagnostic procedure, treatment protocol and preventive measure are discussed. Apart from that this issue also contains 5 original articles, 2 review articles and 2 case reports.

Your opinion and suggestions are highly encouraged us for the development of the journal. The journal is freely available at www.beaconpharma.com.bd for contributing the advancement of public health and medical research.

I do believe this journal will scientifically help doctors in their daily practice.

Dr. G.M. Raihanul Islam
Executive Editor
The Beacon Medical journal

Editorial

Chikungunya Fever(CHIKV) During Pregnancy

Chikungunya fever is a benign form of viral fever caused by an alpha virus that is spread by mosquito bites from the infected Aedes aegypti mosquito. First described during an outbreak of dengue-like illness in the Newala district of the southern province of Tanganiyika (current Tanzania) in 1952–1953[1]. Symptoms of infection are high fever and disabling muscle and joint pain, often associated with a rash and mild bleeding. Persons infected usually recover spontaneously in several days to a week[2]. Fever and arthralgia may occur for several months or even years[3]. There is no significant sex predilection and the virus causes illness in almost all age groups. But pregnant women, the elderly, young children and those with compromised immune systems are in the high-risk categories for being most affected by the Chikungunya virus. The first cases of virus transmission from mother to child at birth were identified in February 2006 during the 2005–2006 outbreak on Réunion Island, France[4]; a total of 38 such cases were reported [5,6]. The virus was also found in specimens from 3 early second trimester miscarriages[7]. Mothers who develop Chikungunya during pregnancy do not transmit any virus to the child. In fact, they can transmit immunity to the child that may last a few years after the birth. If the mother gets infected with Chikungunya just prior to the delivery the virus transmit to the child from the mother due to blood infection during labour.

In the South-East Asia region, Chikungunya virus is maintained in the human population by a human-mosquito-human transmission cycle that differs from the sylvatic transmission cycle described on the African continent. A high vector density is seen in the post monsoon season that enhances the transmission. CHIKV epidemics display cyclical and seasonal trends. There is an inter-epidemic period of 4-8 years (sometimes as long as 20 years). Outbreaks are most likely to occur in post-monsoon period when the vector density is very high. Human beings serve as the Chikungunya virus reservoir during epidemic periods. During inter-epidemic periods, a number of vertebrates have been identified as reservoirs. These include monkeys, rodents, birds, and other vertebrates. The exact nature of the reservoir status in South-East Asia Region has not been documented. After an extensive outbreak during the beginning of current millennium in the French territory of Reunion Islands in the Indian Ocean, the disease has been reported from almost 40 countries from various WHO regions including South-East Asia. During December 2008, an investigation team from the Institute of Epidemiology, Disease Control and Research (IEDCR) and International Centre for Diarrheal Disease Research, Bangladesh (ICDDRB) investigated the first outbreak of CHIKV in the Rajshahi and Chapianawabganj districts of Bangladesh[8], which was in fact the third outbreak[9]. Since May 2017, Dhaka, the capital of Bangladesh had seen 2,700 CHIKV cases, which currently facing a major outbreak of chikungunya. The disease continues to cause epidemics in many countries in the region. As this is an illness not sufficiently covered in medical curriculum, it has become necessary to develop new guidelines, based on the limited clinical experience from managing patients in the region.

Recently, research by the Pasteur Institute in Parishad found a mutation that enables it to be transmitted by Aedes albopitcus (Tiger mosquito), which appears to be the cause of the recent epidemic in Asia. The classic clinical presentation of abrupt high fever (>39^0 C) with severe arthralgia-myalgia and exanthem of maculopapular rash having no feature of severe bleeding, absence of hypotension/shock and thrombocytopenia distinguishes it from dengue.

Most of the patients of Chikungunya infection are symptomatic, has three phases of illness- acute, subacute and chronic course. Joint pain and swelling with severe morning stiffness having symmetrical involvement, involving mostly distal joints. Synovitis or periarticular swelling are present in 32-95% patients, even may have large joint effusion, improves in 1 month, in 15% some persistent joint pain and swelling-morning stiffness may remain more than 3 years[11].

Pregnancy, a situation physiologically oriented toward a Th2-lymhocyte shift, has not been associated as a condition precipitating severe forms of infection in Chikungunya fever (CF). There is no reliable epidemiological data linking chikungunya virus (CHIKV)exposure in the first trimester of gestation to an increased risk for miscarriage, nor to any type of congenital malformation[12,13].

In the second trimester, CHIKV infection has been associated with only three cases of ante partum fetal deaths without clear evidence for the mechanism. The CHIKV crossing of the placenta may be accidental and the timing of the infections (12 weeks + 4 days,and 15 weeks + 5 days) coincides in the woman with the period of deep trophoblast invasion[14]. In the third trimester, although[14] cases of stillborn fetuses have been reported associated with CF in pregnant women cohorts none was positive for CHIKV, which supports the non-permissiveness of the human syncytiotrophoblast to CHIKV. Importantly, CHIKV can be transmitted vertically with a probability ~50%, when the parturient woman has a high viral load during the early stage of labour. Fetal heart rate decelerations are common during labor. The high fever that characterizes chikungunya infection could cause uterine contractions, fetal heart rate abnormalities and meconium-stained amniotic fluid, which might promote spontaneous or induced preterm delivery (cesarean for fetal salvage)[15,16].

Neither postponing delivery nor cesarean has been shown to be protective. The transmission to the neonate is the breakdown of the syncytiotrophoblast due to uterine contractions ("placental breeches" hypothesis) while placental micro transfusion has not been ruled out by a proper scientific investigation. There is no increased risk to the pregnant mother for hypertensive disorders, gestational diabetes mellitus, or intrauterine growth restriction associated with maternal Chikungunya fever[17]. Contrary to dengue, there is also no increased risk for obstetric hemorrhage (placental abruption), preterm birth or low birthweight. Newborn babies infected with Chikungunya are at higher risk for a severe case of the disease.

Diagnostic tests available for Chikungunyaare:

- Detection of antigen and antibody in serum by ELISA test.
- IgM Capture ELISA is necessary to distinguish the disease from dengue fever.

Patients with suspected Chikungunya should be managed as dengue until dengue has been ruled out. There is no specific antiviral drug treatment for Chikungunya. It is a self-limiting disease, treatment is symptomatic and supportive. Treatment is directed primarily at relieving the symptoms; including the joint pain & fever using acetaminophen or paracetamol, NSAIDs such as ibuprofen or as pirinare not recommended during pregnancy, ensuring adequate fluid intake. Aspirin should be avoided due to its effect on platelets. Published evidence does not support the use of corticosteroids, antibiotics or antiviral drugs in the management of CHIKV and indiscriminate use of these agents can be hazardous during pregnancy. Electrolyte imbalance, prerenal acute renal failure, bleeding manifestations should be watched carefully and managed accordingly. Plenty of rest to be ensured.

Acute symptoms typically resolve within 7-10 days. Some patients might have relapse of rheumatologic symptoms (e.g. polyarthralgia, polyarthritis,tenosynovitis) in months following acute illness. Invariable proportions of patients, joint pain may persist for months to years[18]. As there is no vaccine or specific medication available against Chikungunya infection, Vector control is thus very important in controlling or preventing Chikungunya transmission. Elimination of breeding sites or source reduction is an effective method of control. Aedes aegypti is typically acontainer habitat species & breeds primarily in artificial container & receptacles. The best way is to encourage people to eliminate the mosquito habitats by emptying water containers once a week & keeping the permanent water containers covered with a tight-fittinglid. Add a few drops of kerosene oil to open drains, small ponds, and other places where stagnant water remains.Adoption of these methods can be encouraged through community based programs. Legisltion, strong public advocacy & community involvement can also help in vector control. Personal protection like long sleeve loose fitting, light-colored clothes, covering oneself fully, use of unscented shampoo, soap, lotions, and oils use of natural repellents, window nets play limited but useful role[19].

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References

1. Robinson Marion. “An epidemic of virus disease in southern province, Tanganyika territory, in 1952 - 53; I. Clinical Features. Trans Royal Society Trop Med Hyg 1955; 49:28-32.
2. Pialoux G, Gaüzère BA, Jauréguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. Lancet Infect Dis. 2007;7:319–27.DOI PubMed
3. Brighton SW, Prozesky OW, de la Harpe AL. Chikungunya virus infection. A retrospective study of 107 cases. S Afr Med J. 1983;63:313–5.PubMed
4. FritelX et al. Chikungunya Virus Infection during Pregnancy, Réunion, France, 2006. Emerging Infectious Diseases Journal March 2010;16:1
5. Robillard PY, Boumahni B, Gérardin P, Michault A, Fourmaintraux A, Schuffenecker I, Vertical maternal fetal transmission of the chikungunya virus. Ten cases among 84 pregnant women [in French]. Presse Med. 2006;35:785–8.-DOIPubMed
6. Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, Mother-to-child transmission of chikungunya virus infection. Pediatr Infect Dis J. 2007;26:811–5.DOIPubMed
7. Touret Y, Randrianaivo H, Michault A, Schuffenecker I, Kauffmann E, Lenglet Y, Early maternal-fetal transmission of the chikungunya virus [in French]. Presse Med. 2006;35:1656–8
8. ICDDR B: First identified outbreak of chikungunya in Bangladesh, 2008.Health Sci Bull 2009, 7:1.
9. Chowdhury FI, Kabir A, Das A, Mukerrama SM, Masud S. Chikungunya fever:

an emerging threat to Bangladesh. J Med 2012;13:60–64.

10. WHO (2008). Guidelines on Clinical Management of Chikungunya Fever.
11. Burt F J, Chen W, Miner J J, et al. (2017). Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. Lancet Infect Dis; 17: e107–17.
12. Saito S, Sakaï M. Th1/Th2 balance in preeclampsia. J Reprod Immunol 2003; 59: 161–173. doi: 10.1016/S0165-0378(03) 00045-7.
13. Ceccaldi PF, Longuet P, Mandelbrot L. Infections virales émergentes et grossesse. Gynecol Obstet Fertil 2007;35:339 –342.doi:10.1016/j.gyobfe.2007.02.020
14. Her Z, Teng TS, Tan JL, et al. Loss of TLR3 aggravates CHIKV replication and pathology due to an altered-virus specific neutralizing response. Embo Mol Med 2014; 7:24–41. doi: 10.15252/emmm.201404459.
15. Carles G, Talarmin A, Peneau C, Bertsch M. Dengue fever and pregnancy. A study of 38 cases in French Guiana [in French]. J Gynecol Obstet Biol Reprod (Paris). 2000;29:758–62.PubMed
16. Waduge R, Malavige GN, Pradeepan M, Wijeyaratne CN, Fernando S, Seneviratne SL. Dengue infections during pregnancy: a case series from Sri Lanka and review of the literature. J Clin Virol. 2006;37:27–33.DOIPubMed
17. Zhang J, HWei, D Wu, Tian Z. Toll-like receptor 3 agonist induces impairment of uterine vascular remodeling and fetal losses in CBA DBA/ 2 mice. J Reprod Immu nol 2007; 74: 61–67. doi: 10.1016/j.jri.2006.10.005
18. Chen CI, Clark DC, Pesaveto P, et al. Comparative pathogenesis of epidemic and en zootic chikungunya viruses in pregnant Rhesus macaque model.Am J Trop Med Hyg 2010; 83: 1249–1258. doi: 10.4269/ajtmh.2010.10-0290.
19. Disease control division, Directorate general of health services, Ministry of health & family welfare, Bangladesh. National guideline onclinical management of Chikungunya fever. 2017:1-24.

Original Article

Thrombocytosis: A Paraneoplastic Syndrome In Patients With Hepatitis B Related Hepatocellular Carcinoma

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ABSTRACT

Background: *The highest incidence of Hepatocellular carcinoma (HCC) is in Asia, accounting for about 76% of all cases worldwide. In South East Asia, hepatitis B is the most common underlying cause. HCC patients manifest a variety of paraneoplastic syndromes. Thrombocytosis was reported in children with hepatoblastoma.*

Objectives: *The aims of this study was to find out the relationship of thrombocytosis with the hepatitis B-related hepatocellular carcinoma.*

Methods: *This observational study was carried out in the Department of Hepatology, BSMMU from January 2012 to December 2013. The study was approved by the Ethical Institutional Review Board (IRB) of BSMMU, Dhaka. The diagnosis of HCC was confirmed by pathological examination or AFP elevation (400ng/ml) combined imaging (CT/MRI) and diagnosis of thrombocytosis was made by platelet count >450×10^9/mm^3. All images were evaluated by 2 trained radiologists by consensus after exclusion of hepatitis C virus infection (Anti HCV+ve) and significant alcohol intake (>20 gm/day). All patients were HBsAg positive done by ELISA test.*

Results: *A total 44 patients were included in this study. Among them, 91% were male (n=40) and 09% were female (n=4).The mean age was 48.2 (±12.9) years with range from 23 to 80. Cirrhosis was 79.5% (n=35) and no cirrhosis was found 20.5% (n=9). Thrombocytosis was found 6.8% (n=3). Among thrombocytosis, cirrhosis and non-cirrhosis were 66.6% (n=02) and 33.4% (n=01) respectively. Mean α-fetoprotein (ng/mL) was higher in HCC patients without thrombocytosis than HCC patients without thrombocytosis (39370 vs 13476,P value .036).*

Conclusions:*Thrombocytosis is one of the paraneoplastic syndromes in patients with HBV related HCC. HCC patients with thrombocytosis are associated high serum AFP level.*

Keywords: *Hepatitis B virus; thrombocytosis; Hepatocellular carcinoma.*

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Introduction

HCC is the sixth most common malignant tumor and the third most common cause of cancer deaths worldwide[1]. The etiological agent of HCC is known in more than 90% of cases. In South East Asia, hepatitis B is the most common underlying cause. The highest incidence of HCC is in Asia, accounting for about 76% of all cases worldwide[2]. HCC is the common malignancy in Bangladesh. During its clinical course, patients may manifest a variety of paraneoplastic syndromes, including hypercholesterolemia, hypoglycemia, hypercalcemia, and erythrocytosis[3].According to previous reports, the prevalence of paraneoplastic syndromes was 11.4-12.1% for hypercholesterolemia, 2.8-5.3% for hypoglycemia, 1.8-4.1% for hypercalcemia, and 2.5-3.1% for erythrocytosis[4-6]. Thrombocytosis has been found in children with hepatoblastoma and other malignancies[7]. Based on this hypothesis, we find out the relationship of thrombocytosis with the hepatitis B-related hepatocellular carcinoma.

Methods

Study Population

This is a hospital based observational study of 44 HCC patients. Patients with HBsAg positive done by ELISA test and features suggestive of HCC attending at outpatient & inpatient department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2012 to December 2013 is enrolled this study. Aims and objectives along with its procedure, risks and benefits of this study were explained to the patients and attendants in easily understandable local language (Bangla) and then informed written consent was taken from each participant. Prior to the commencement of the study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU.

Patients were divided into two groups. Group A (HCC patients with thrombocytosis) and Group B (HCC patients without thrombocytosis).The inclusion criteria were: HCC patients were recruited prospectively.The diagnosis of HCC was confirmed by α-fetoprotein elevation (≥400 ng/ml) combined with computed tomography (CT) and/or magnetic resonance imaging (MRI) or Pathological examination (Biopsy/FNAC) [Figure 1] and diagnosis of thrombocytosis was made by platelet count >450 x

$10^9/mm^3$. All images were evaluated by 2 trained radiologists by consensus. Exclusion criteria were alcohol abuse (>20g/day), evidence of acute infections or gastrointestinal bleeding, polycythemia vera and infection with HCV (anti-HCV positivity).

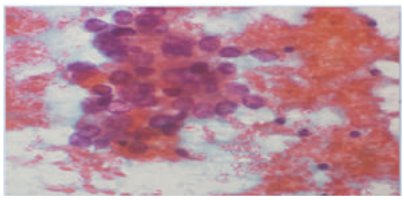

Figure 1: Cytopathic feature of Hepatocellular carcinoma (Haematoxylin and eosin stain, Courtesy: Department of Pathology, BSMMU). ID no:18

Procedure for fine needle aspiration (FNA) from liver space occupying lesions SOL(s) After taking informed written consent, patients laid with empty bladder. The site was painted with iodine solution and draped. Skin and deeper tissue was infiltrated with local anesthesia (2% xylocaine) at the proposed puncture site using a 23 G needle. Under real-time USG guidance and using 22 G disposable spinal needles the cavity was entered and aspirated material was collected. The prepared glass slides were fixed with 95% ethanol and kept in Kaplan's jar after labeling. Samples were sent for cytopathological examination to the Department of Pathology, BSMMU. Dressings were applied at the needle puncture sites and patients were followed up for next 6 hours.

Statistical Analysis

All data was recorded systematically in a preformed data collection sheet and quantitative data expressed as mean ± SD.Qualitative data analyzed by chi square test and quantitative data by student's T test or Mann Whitney's U test. Differences in laboratory parameters compared using one-way ANOVA.P value of ≤ 0.05 was considered to be statistically significant. All statistical computations were performed by using SPSS version 20 (Statistical Package for Social Science).

Results

Demographic and laboratory characteristics

Table 1: Comparison of clinical and laboratory data between hepatocellular carcinoma (HCC) patients with and without thrombocytosis

	HCC patients with thrombocytosis (n = 03)	HCC patients with thrombocytosis (n = 41)	P value
Age (yr)	47±12	48.3±13	0.001
Sex (male: female)	2:1	38:3	0.130
Mean platelet counts ($10^9/mm^3$)	499.33±45	213.63±89	0.037
Median (range)	510 (450-528)	120 (10-440)	
Hb% (g/dL)	12±1.2	11.4±1.7	0.008
Prothombin time	15.9±1.8	15.1±2.2	0.011
Albumin (g/dl)	2.9±.5	3.03±.63	0.003
Cirrhosis (+ :-)	2:1	33:8	0.507
Splenomegaly (+ :-)	2:1	24:17	0.782
Portal vein thrombosis (+ :-)	1:2	17:24	0.782
Mean α-fetoprotein (ng/mL)	39370±12835	13476±17102	0.036
Median (range)	34112 (30000-540000)	2230 (9-50000)	
BCLC stage (0,A,B,C&D)	0,0,0,1&2	1,1,1,10&28	0.002

Data were expressed as mean±SD. BCLC: Barcelona Cancer Liver Clinic

In comparison of the clinical and laboratory data between HCC patients with thrombocytosis and those without, HCC patients with thrombocytosis were significantly younger in age, had a higher mean serum AFP level, more progressive BCLC stage were less likely to be suitable for HCC therapy than those without thrombocytosis (Table 1). There were no significant differences in sex distribution, rates of cirrhosis. Splenomegaly and PVT between the two groups.

Among the 44 HCC patients 03 (6.8%) had thrombocytosis (mean platelet count 499.33±45×10^9/mm3, range 450-528×$10^9/mm^3$). The mean serum AFP level was 39370±12835 ng/mL (median 34112 ng/mL, range 30000-540000 ng/mL) in thrombocytosis group.

Table 2: Distribution of the study population by age range (n = 44)

Age range	Frequency	Percent	Cumulative Percent
< 20	01	02.3	02.3
21 -30	05	11.4	13.7
31- 40	11	25.0	38.7
41- 50	11	25.0	63.7
51- 60	10	22.7	86.4
> 60	06	13.6	100.0
Total	44	100.0	100.0

Table II shows distribution of the study population by age range. Maximum (50%) patient's ages were belonged to 35-55 years. The mean age was found 48.20 ±12.92 years with range from 18 to 80 years. The mean age difference was statistically significant (P = 0.001) between two groups.

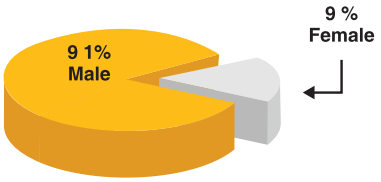

Figure 2. Gender distribution of the study population (n= 44)

Figure 2 shows male gender was predominant 91% (40) of the study population. Male female ratio was 10:01. Male was also predominant in both groups, which were 66% (02) in thrombocytosis with HCC group and 92.7% (38) in thrombocytosis with HCC group. The difference was not statistically significant (P = 0.13) between the two groups.

Distribution of thrombocytosis in the study population

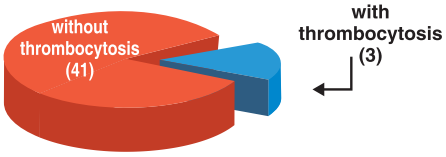

Figure 3: Distribution of thrombocytosis in the study population (n=44)

Figure 3 shows thrombocytosis in the study population. Among 44 patients 03(6.8%) was thrombocytosisand 41 (93.2%) was normal platelet count.

Discussion

This is the study from Bangladesh in which the characteristics of HBV related HCC have been studied. HBV infection accounts for most primary HCC and treating HBV infection substantially reduces the risk of HCC development. Chronic

HBV infection is recognized as the most important causal factor for HCC in humans.

The incidence of HCC increases with age. The development of HCC is uncommon before 40 years of age in western world. However, the pattern of HCC incidence by age is sometimes dependent on the geographic pattern or on etiologic factors .The age distribution of patients with HCC in the present study was similar to other studies in past. Studies from Bangladesh (M Khan et al & Gani ABMS et al),India (Sarma MP et al) and Pakistan (Abbas Z et al) have shown the maximum incidence of HCC in the fifth to sixth decade[8-11]. The male preponderance is similar to our previous Bangladeshi study and other studies from India and Pakistan[8-11].The population-based data show a male to female ratio of 3:1–2:1. 1.22 However, high preponderance of HCC in males reported in hospital-based data could suggest a gender bias in seeking medical treatment.

Common paraneoplastic syndromes seen in HCC patients include hypercholesterolemia, hypoglycemia, hypercalcemia, and erythrocytosis[1]. Thrombocytosis has been reported in children with hepatoblastoma[7]. The prevalence of thrombocytosis in HCC patients has not been previously reported. Our results showed that 6.8% of HCC patients had thrombocytosis which was defined as a platelet count >450× $10^9/mm^3$. The prevalence of thrombocytosis might be underestimated because most HCC patients were associated with liver cirrhosis, and thrombocytopenia was frequently seen in these patients.

The clinical significance of thrombocytosis in HCC patientswere similar to HCC patients with other paraneoplastic syndromes, including hypercholesterolemia, hypoglycemia, hypercalcemia, and erythrocytosis[3-6]. High serum AFP, more progressive BCLC stage and poor prognosis have been identified in HCC patients with thrombocytosis. Human thrombopoietin (TPO), a glycoprotein hormone also known as megakaryocyte growth factor, is known to play a key role in the development of the growth and maturation of megakaryocytes and platelet production[12].TPO is secreted principally by hepatocytes and bone marrow stromal cells[12-13]. The relationships between serum TPO levels and platelet counts in HCC patients, especially those associated with thrombocytosis, are of clinical interest.The main sites of TPO production are the liver and to a lesser degree the kidneys, bone marrow and spleen.

Messenger RNA transcripts of TPO have been found mainly in the liver and released into circulation[13]. Most TPO is bound with and degraded by circulating platelets and megakaryocytes in the bone marrow, and the serum level is low. Circulating TPO levels are inversely correlated with the number of TPO receptors (c-Mpl-molecules) in regulating megakaryocytopoiesis and platelet production.When thrombocytopenia develops, binding receptors decrease and serum TPO levels increase. Elevated TPO levels stimulate megakaryocytopoiesis and result in increased platelet production[14-16]. Patients with cirrhosis were frequently associated with low platelet counts. However, serum TPO levels in cirrhotic patients were found to be lower than chronic hepatitis patients or normal subjects due to inadequate TPO production by the diseased livers[17]. HCC patients with thrombocytosis had a significantly higher mean serum TPO level than HCC patients without thrombocytosis. In addition, the platelet counts and serum TPO levels in HCC patients with thrombocytosis dropped after a surgical removal of the tumor or TACE, and relevated when a tumor recurred. Changes of platelet counts and serum TPO levels were parallel to the changes of serum AFP[18]. The mechanisms of thrombocytosis in HCC patients are similar to those for other paraneoplastic manifestations. Hypoglycemia has been related to the overproduction of insulin-growth-factor II with insulin-like activities[3-6]. The cause of hypercalcemia has been related to overproduction of a parathyroid-related protein which interacts with parathyroid hormone receptors[4]. Elevation of serum erythropoietin has been seen in HCC patients with erythrocytosis[5,19].

Conclusion

In conclusion, thrombocytosis is one of the paraneoplastic syndromes in patients with HCC, due to the overproduction of TPO by HCC. HCC patients with thrombocytosis are associated with a high serum AFP level. Limitation of this study is its small sample size and single center.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

Reference

1. Jemal A, Bray F, Center MM, Ferly J, Ward E & Forman D. Global cancer statistics.CA Cancer J Clin 2011; 61:69-90.
2. Bosch FX, Ribes J, Cléries R & Diaz M. Epidemiology of hepatocellular carcinoma. Clin. Liver Dis. 2005 ; 9(2): 191 – 211. 3.
3. Okuda K, Kondo Y. Primary carcinomas of the liver. In: Haubrich WS, Schaffner F, Berk JE, eds. Gastroenterology Volume 3.5th ed. Philadelphia:W.B. Saunders 1995: 2467-2468.
4. Hwang SJ, Lee SD, Chang CF, Wu JC, Tsay SH et al.Hype cholesterolemia in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 1992; 7: 491-496
5. Yen TC, Hwang SJ, Wang CC, Lee SD, Yeh SH. Hyper calcmia and parathyroid hormone-related protein in hepato cellular carcinoma. Liver 1993; 13: 311-315.
6. Hwang SJ, Lee SD, Wu JC, Chang CF, Lu CL, Tsay SH, Lo KJ. Clinical evaluation of erythrocytosis in patients with hepatoce lular carcinoma. Chin Med J 1994; 53: 262-269.
7. Nickerson HJ, Silberman TL, McDonald TP. Hepatoblastoma, thrombocytosis, and increased thrombopoietin. Cancer 1980; 45: 315-317.
8. Khan M, Haq SA, Ahmed N & Matin MA. Etiology and Clinical Profile of Hepatocellular Carcinoma in Bangladesh. Bangladesh Med. Res. Counc. Bull. 1997; 23(1): 16-24.
9. Gani ABMS, Al-Mahtab M, Rahman S, Akbar SMF. Characte istics Features of Hepatocellular Carcinoma in Bangladesh and their Public Health Implications. Euroasian J Hepato-Gastroenterol 2013; 3(1):28-30.
10. Sarma MP, Asim M, Medhi S, Bharathi T, Diwan R, and Kar P 2012.Viral Genotypes and Associated Risk Factors of Hepato cellular Carcinoma in India. Cancer Biol Med ; 9 (3): 172-181.
11. Abbas Z, Siddiqui AU, Luck NH, Hassan M, et al. Prognostic factors of survival in patients with non-resectable hepatocellular carcinoma: hepatitis C versus miscellaneous etiology. J. Pak. Med. Assoc. 2008; 58(11):602-7.
12. De Sauvage FJ, Hass PE, Spencer SD, Malloy BE et al.Stimu lation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 1994; 369: 533-538.

13. Martin TG, Somberg KA, Meng YG, Cohen RL et al. Thrombo poietin levels in patients with cirrhosis before and after orthot opic liver transplantation. Ann Intern Med 1997; 127: 285-288

14. McCarty JM, Sprugel KH, Fox NE, Sabath DE, Kaushansky K. Murine thrombopoietin mRNA levels are modulated by platelet count. Blood 1995; 86: 3668-3675.

15. Cohen-Solal K, Villeval JL, Titeux M, Lok S, et al.Constitutive expression of Mpl ligand transcripts during thrombocytopeni or thrombocytosis. Blood 1996; 88:2578-2584.

16. Eaton DL, de Sauvage FJ. Thrombopoietin: the primary regulator of megakaryocytopoiesis and thrombopoiesis. Exp Hematol 1997; 25: 1-7.

17. Peck-Radosavljevic M, Zacherl J, Meng YG, Pidlich J et al. Is inadequate thrombopoietin production a major cause of throm bocytopenia in cirrhosis of the liver? J Hepatol 1997; 27: 127-131.

18. Hwang SJ, Luo JC,Li CP, Chu CW et al. Thrombocytosis: A paraneoplastic syndrome in patients with hepatocellular carcinoma World J Gastroenterol 2004;10(17):2472-2477.

19. Kew MC, Fisher JW. Serum erythropoietin concentrations in patients with hepatocellular carcinoma. Cancer 1986; 58:2485-2488.

Original Article

Oligohydramnios At Term-A Clinical Presentation and It's Outcome

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ABSTRACT

Background: *Obstetrician providing health care often face a situation in which pregnant women is noted to have oligohydramnios both clinically and sonographically. So the purpose of this study is evaluation of the clinical presentation and perinatal outcome of pregnancy associated with oligohydramnios.It would help in identifying patient at risk and of taking appropriate measures about the mood,date and time of delivery and about neonatal care.*

The Aim of Study: *To find out the feto-maternal outcome of patients having oligohydramnios at term.*

Patients and Methods: *A prospective institutional observational study was conducted in Department of Obstetrics and Gynecology, Dhaka Medical College and Hospital, Dhaka, Bangladesh over a period of six months from January to June, 2009. Fifty patients having oligohydramnios diagnosed by USG was the target population. With close follow up the mode of delivery of the patients was noted whether normal vaginal delivery or assisted vaginal delivery or caesarean section was required. During delivery color and amount of liquor was noted.After delivery close surveillance of fetus and placenta was done. APGAR score at 1 minute and 5 minutes, birth weight of baby, any congenital anomaly and any neonatal complication such as meconium aspiration syndrome, respiratory distress syndrome, sepsis, NICU admission, stillbirths or perinatal deaths was recorded. With proper examination of placenta size, shape, calcification any abnormality of placenta was recorded.*

Result: *Fifty admitted women met the inclusion criteria of which 66% had AFI 5.1-8 cm and 34% has AFI<5 cm.Rate of caesarean delivery were significantly higher is AFI<5 (severe oligohydramnios) group compared with the AFI>5cm. No vaginal delivery in severe oligohydramnios group. Caesarean delivery for fetal distress also occurred significantly (52.94%). This study showed high rate of low birth weight baby (<2.5kg in 76% patients) APGAR score <5 is found in 52% patients in first minute. Neonatal complication occurred in 32 babies among 50 babies. Admission in neonatal ward is needed in 41.30% babies which is significantly high. Congenital anomaly is found in 6% babies.*

Conclusion: *This study was done to findout the perinatal outcome of patients having oligohydramnios at term. Caesarean section rate was significantly in women with oligohydramnios and indication of caesarean section was mainly due to fetal distress. APGAR score below 7 and low birth weight baby was significantly higher in women with oligohydramnios. Pregnant women associated with oligohydramnios has shown a significant impact on perinatal mortality and morbidity.*

Key Words: *Oligohydramnios, APGAR score.*

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Introduction

There is vital need for a non restricting intrauterine environment which develops before the fetus. Every fetus is surrounded by a protective cushion of amniotic fluid whether the fetus develops inside the mother as a viviparous species or in an egg[1]. The mechanism of amniotic fluid production and turn over are complex . It is produced soon after the amniotic sac forms at about 12 days after conception which is necessary for its proper growth and development. It cushions the fetus from physical trauma, permits fetal lung growth and provides a barrier against infection[2].

By the second trimester amniotic fluid is being produced primarily through fetal urine production and primarily reabsorbed through fetal swallowing. Significant amount of amniotic fluid is also produced and reabsorbed by the fetal lung[3,4] Significant amount of also produced by transudation from maternal serum across the fetal membranes or from maternal circulation in the placenta[2]. Amniotic fluid volume is affected by the status of maternal hydration and maternal plasma osmolarity[4,5]. The normal amniotic fluid volume increases with gestational age, peaking at 800-1000ml, which co insides with 36-37 week gestation.

AFV increases steadily throughout most of pregnancy, with a volume of about 30 ml at 10 weeks and a peak of about 1L at 34-36 weeks gestation. AFI decreases in the late third trimester, with a mean of AFV of 800 ml at 40 weeks[6].

Amniotic fluid can be assessed qualitatively or quantitively by ultra sound.The quantitative method measure single pocket >2cm the most common quantitative measure in clinical practice is AFI (amniotic fluid index). The AFI was introduced in 1987 to replace the 2 cm pocket technique of fluid assessment[7]. In USG normal amniotic fluid index <8 cm (below 5th percentile) or > 24 cm (above 95th percentile) was considered abnormal at gestational age 28-40 weeks.

Oligohydramnios is defined as AFI<5 cm8. Clinically in oligohydramnios uterus size is smaller than the period of amenorrhoea, the uterus is full of fetus because of scanty liquor. Chromosomal abnormalities, structural malforma-

tions, malformation of urogenital system are commonly associated with oligohydramnios that adversely affect the perinatal outcome. In renal agenesis oligohydramnios is most common due to decreased fetal urine production.Moreover oligohydramnios also related to abnormal heart rate, caesarean delivery, IUGR and cord compression [9-14].

Oligohydramnios is associated with 4.5% of all pregnancies and severe oligohydramnios is a complication in 0.07% of pregnancies[15]. Bangladesh is one of the developing countries of the world, where disease poverty illiteracy and malnutrition are common. In our country there is high prevalence of pre-eclampsia,intrauterine growth retardation[16], premature rupture of membrane and all this conditions are associated with oligohydramnios. Facilities for intra uterine fetal monitoring is very limited in our country and without proper assessment of fetal condition, we often go for operative procedure with added risk to fetus and mother. Reliable studies to predict perinatal outcomes at term are not available in our country. Through this study Iwould like to assess the mode of delivery and outcome in patients with oligohydramnios at term.

Materials and Methods

This prospective institutional observationalstudy was done from January'2009 to June'2009 in the Department of Gynecology and Obstetrics, Dhaka Medical College Hospital, Dhaka, Bangladesh. About fifty pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion criteria. A written informed consent was taken from eligible women on admission. The study protocol was approved by the ethical committee of Dhaka Medical College Hospital, Dhaka, Bangladesh.Inclusion criteria were women with a clinically suspected then sonographically confirmed cases of oligohydramnios with single live pregnancy undergoing delivery above 37 weeks or greater gestational age (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report). Exclusion criteria were pregnancy having normal amniotic fluid volume,polyhydramnios, placenta previa, multiple gestation, placental abruption (determined by history and ultrasound report) hypertensive disorders in pregnancy, preeclampsia, and known case of cardiac, renal, liver diseases, epilepsy, moderate anemia and unwilling to participate in the study.

Data were collected by investigator herself by questionnaire and relevant data were collected in a data sheet. Collected data were compiled, edited and analyzed by simple statistical method.

Results

Fifty admitted women met the inclusion criteria of which 66% had AFI 5.1-8 cm and 34% has AFI<5 cm. Rate of caesarean delivery were significantly higher is AFI<5cm (severe oligohydramnios)group compared with the AFI>5cm. No vaginal delivery in severe oligohydramnios group.Caesarean delivery for fetal distress also occurred significantly (52.94%).This study showed high rate of low birth weight baby (<2.5kg in 76% patients) APGAR score <5cm is found in 52% patients in first minute.Neonatal complication occurred in 32 babies among 50 babies. Admission in neonatal ward is needed in 41.30% babies which is significantly high. Congenital anomaly is found in 6% babies.

Discussion

The aim of my study was to assess the perinatal outcome of the patients having oligohydramnios at term. Assessment of amniotic fluid volume in antenatal period is a helpful tool in determining who is at risk for potentially adverse perinatal outcome. In my study mean age of the patients was 27.62±3.66 years. This study showed oligohydramnios was higher in multiparous women.

Studies done by Magannet al[33], Chauhan[9], Cosey etal[13], there was no relation of age and parity with oligohydramnios. In my study higher incidence of multiparous women was probably due to small sample size and most of the patients were found multiparous.

In my study among the clinical presentation most common clinical presentation is lower symphysiofundal height (96%) and other clinical presentations are anaemia and lower abdominal girth at term below expected.

Kennath F, Trofatter Jr in there study found 3 primary reason of little amniotic fluid; rupture membrane, fetal anomaly and placental abnormalities.Spontaneous rupture of membrane can occur any time during pregnancy. Most of the times membrane remain intact until onset of labour. The most common but most serious cause of oligohydramnios is fetal congenital anomaly, mostly by abnormalities of fetal kidney and urinary tract. Conditions causing maternal dehydration may lead to severe oligohydramnios such as dehydration caused by diarrhea, hyperemesis and severe pre-eclampsia. Placenal insufficiency due to any reason may lead to oligohydramnios like severe pre-eclampsia, IUGR.

In my study most common cause found is PROM(48%). Other causes are severe pre-eclampsia,congenital anomaly (16% and 6%) respectively. But in 30% cases cause can not be indentified probably because of lack of facilities.

In my study among 50 pts only 12 patients had meconium stained liquor which was 24%. In Cosey's[13] study among 147 oligohydramnios patients meconium stained liquor was found only in 9 patients,which was only 6%. He stated that meconium stained liquor less often complicate the pregnancy with oligohydramnios. This study showed no obvious relation between meconium stained liquor and oligohydramnios. But Chhabras's[17] study showed 38% retrospective and 31.5% of prospective cases were complicated by intrapartum meconium. Magann at el[21] found that more the degree of oligohydramnios, more the chance of liquorstained and more chance of meconium aspiration syndrome(22% in our study and 6% in Cosey's study)

In this study caesarean section rate was 68% which is significantly higher and among indication of caesarean section fetal distress was significantly higher(75%). Chauhan et al[9] found that the AFI ≤ 5cm was associated with increased incidence of caesarean section delivery for fetal distress. Anna et al[34] found 15.2% caesarean section delivery among 341 oligohydramnios patients. Voxman[35] also found increased rate of caesarean section(14.7%)for fetal distress in oligohydramnios group. Ina case control study by Conway36, 183 low risk term patients with oligohydramnios were matched to 183 women of similar gestational age and parity who presented in spontaneous labour. The patients with oligohydramnios were induced and showed an increased caesarean delivery rate. But the increased rate was not due to fetal distress but was attributed to

the induction process. In Anna et al[22] study and Voxman[35] study caesarean section rate is higher but not significantly higher as it is found in this study. It was due to our fewer facilities for antepartum and intrapartum fetal monitoring. So far the avoidance of adverse perinatal outcome in most cases caesarean section was done.

In Voxman study 35 caesarean section rate was higher in severe oligohydramnios group than in borderline oligohydramnios group in this study we also found that caesarean section delivery was significantly higher in severe oligohydramnios than borderline oligohydramnios group and we had no vaginal delivery in severe oligohydramnios.

This study showed significantly higher rate of low birth weight baby. In a study done by Magannet al[33] among 79 oligohydramnios patients 41(35%)had low birth weight baby. Oligohydramnios may be a reflection of poor intrauterine nutrition to the fetus. Roberts[36] found increased IUGR in term oligohydramnios patients.

In this study APGAR score <5 in 1st min found in 52% patients and APGAR score<7 in 5th minute was found in 32% patients. A recent study by Megann EF[37] failed to detect any difference in the incidence of non reacting non stress tests,meconium stained amniotic fluid, caesarean delivery for fetal distress, low APGAR scores when oligohydramnios is present.

In my study neonatal complications occurred in 24 babies among 50 babies. Respiratory distress syndrome was 12% in the study. In Cosey's study respiratory distress syndrome was 10%. Injudicious home trial with uterotonic drug may be the cause of slightly higher rate of respiratory distress.

In Cosey's study meconium aspiration syndrome was 1.4% where in my study meconium aspiration syndrome was 22%. This higher rate may be due to higher rate of hypertensive disorder in pregnancy causing oligohydrmnios due to lack of antenatal check up.

Our study showed that there was only one neonatal death. The baby was born in Rh incompatibility. We had one still born baby. Birth weight of that baby was 2.6kg, amniotic fluid was meconium stained and there was a true knot in the cord. The cause of intrauterine death may be placental insufficiency due to hypertensive disorder of pregnancy. All these two babies were delivered by vaginal route.

In our study we found three babies with congenital anomalies. Chhabras[17] found perinatal mortality rate in cases of oligohydramnios was 87.7 and 4.15% babies had congenital anomalies.

Conway[36] and Zhang[38] found no significant difference neonatal outcome in oligohydramnios patients compared with normal liquor volume.

In our study admission in neonatal care unit was 41.30% significantly high. Neonatal admission in two other studies were 10% (Cosey's[13]) and 7% (Chauhan[9]) respectively.

Conclusion

Oligohydramnios was more common in multiparous women and lower symphysiofundal height is most common clinical presentation. In this study PROM was the most common cause found. Caesarean section delivery was higher in women with oligohydrmnios and indication of caesarean section was mainly due to fetal distress. In our study we found that both neonatal morbidity and APGAR score below 5 in 1st minute were high in oligohydramnios group.

References

1. Kneeppet RA, Maternal – Placental fetal Unit, fetal & early neonatal physiology in Dechrver AH, Nathan L Current obstetric and Gynecologic diagnosis of treatment 10th ed. USA: MC Graw hill, 2007, 159-186.
2. Queenan JT. Polyhydramnious and Oligohydramnios. Management of High risk pregnancy. 4th edition 1999, USA: Black - well science 421-431.
3. Kill Patrick SS, Safford KL. Meternal hydration increases amniotic fluide index in women with normal amniotic fluid. Obstectgynecol 1993.81: 49-52
4. Chandra pc, Schianello HS, Lew andowshi MA. Effect of oral and intravenous hydration on oligohydramnios J Repord Med 2000.45; 337-340
5. Aneda Umbar and M Arshedchohen, intravenous Meternal hydration in third trimester oligohydramnios effect on amniotic fluid volume. Department of obs&Gyn, Lady, Willing Don Hospital Lahore 2007; 17 (6); 336-339
6. Boy RL Polyhydramnios and oligohydramnios, Available at, Url: http://www. Emedicine. Com/PED/topic 854
7. Phelan JP, Smith CV, Broussard P, Small M Amniotic fluid Volume assessment with the four quadrant technique at 36-42 wks gestation. J Repord Med 1987;32;540-542.
8. Carrphylli 3 L Recciotti, Hope, Freund, Karan , Scott Kahan (2003), In a page ob/gy&womens health Cambridge MA, Black well publishers, pp.105.
9. Chauhan SP, Sauderson ,Hendrive NW, Magann EF, Devoe LP, Perinatal outcome and amniotic fluid index in antepartum and intrapartum periods, a meta analysis. Am J obstet gynecol-1999;181:1475-1478.
10. Chamberiain PF Manning FA. Morrison I et al. Ultrasound evaluation of amniotic fluid volume. The relationship of marginal and decreased amniotic fluid volumes to perinatal outcome, AM J uk/showdic/40024667/38k, September 26.2009
11. Moore TR. Clinical assessment of amniotic fluid, Clinobstedgynecol 1997;303-313.
12. Banks EH. Perinatal risk associated with borderline amniotic fluid index. Am J obstetgynecol 1999;180;1461-1463.
13. Cosey BM. Pregnancy outcome after antepartum diagnosis of oligohydramnios at or beyond 34 weeks gestation. Am J obstedgynecol 2000.
14. Rainford M. Adair R, Scialli AR, Ghidine A, Spong CY. Amniotic fluid index in the uncomplicated term pregnancy, prediction of outcome. J Repord Med 2001; 46;589-592.
15. Luton D, Alran S, Fourchottev, et al paris is heat wave and oligohydramnios, Am obstegnynecol 2004 december 191 (6) 2013-5 (abstruct)
16. Moses J, Doherty D, Magan E, Chauhan S, Morrision J. A randomized clinical trial of the intrapartam assessment of amniotic fluid index various the single deepest pocket technique. Am J obstetgynecol 2004, 190;1564-1570.

17. Ehhabras, paryan R, Bawashar R, 304 Oligohydramnios a potential market for serious obstetric complication. J obs let gynecol 2007.

18. Dutta DC. A text book of obstetrics, seventh edition 2011.

19. WhitnyWillams, amniotic fluid, objections with narration and illustration.

20. 2Queenan JT, Vongal H and Kubarych SE. Amniography for clinical evaluation of erythroblastosis foetalis. Am J obstetGynaecol 1998, 102:264.

21. Amniotic fluid and biophysical profile http://www.gynob.com/biopamfl.htm -september 30, 2009.

22. Alan H Decherney, lauren Nathan, T Murphy, Goodein-Leufer, The Amniotic fluid and prolonged pry, Corresponds Diagnosis and obstretrics&gynaecology 10th edition, 184-1.85 2082, 292, 30g.

23. Elliot PM, Inman WHW. Volume of liquid amnii in normal and abnormal pregnancy. Lancet 1995, ii, 836.

24. Pritchard JA. Deglutition by normal and anencealic fetuses, obstetGynecol 1995, 25;289.

25. Abramouich PR, Page kp. Pathway of water transfer between liquor amnii and the fetal placental unitat term Eur J obstetgynecol 1973;3:155.

26. Lin dt, BilleWicz WZ and Cheyne GA. Composition of amniotic fluid and meternal blood throughout pregnancy. J obstetGynecol Br Common W 1988; 178:505.

27. Gillert WM, Brace RA. The missing link in amniotic fluid volume regulation, Intra membranes absorption. ObstetGynecol 1989;74:748.

28. Alberto Bacehi Modena, Stefaninfieni (Department of obstetrics, Gynecology and Neouatology) University of Prema, Amniotic fluid Dynamics.

29. Practicle guide to high risk pregnancy and peliuery, Third edition, August 2007.

30. Nricovolanto, Dandolo, Grmellini, Sabrina Moretti, Christine kaihura, Giulio Bevilacqua, Alteration of the amniotic fluid and neonatal outcome (Amniotic fluid, polyhydraminos, Oligohydramnios) ACTA BIO MEDICAL ATENEO PARMENES 2004; 75 suppl. 71-75 @ Mattioli 1885.

31. Ferndo Arias Shirish N, Daftary, Amaranths G Ethide Prolonged pregnancy and multifetal gestation. Practical guide to high risk pregnancy and delivery. 30 edition 2009, 278-300.

32. APA discussion forum (low amniotic fluid level oligohydramnios American pregnancy) complication of low amniotic fluid level in oligohydramnios. William obstetrics Second ed, Cu Cunningham F-gray et el.ch21 March of deimeshttp://Marchofdines.com.

33. Magsnn EF, Kinsella JM. Chauhan SP, McNamanra MF, Gehring BW and Morison JC. Dose an amniotic fluide in less than 5 necessitate delivery in high risk pregnancies. A case control study.

34. Locatelli A, vergani P, Pezzullo JC. Toso L and Verderio M. P Perinatal outcome associated with oligohydramnios in uncomplicated pregnancies. Arch gynecolobsted 2004;269;130-3.

35. Voxman EG, Trail S and Wing BA. Low amniotic fluid as a predictor of adverse perinatal outcome. Journal of perinatology 2002;22282-5.

36. 3 Conway DL et al. isolated olygohydrannios in the term pregnancy. It is a clinical entity. J Marten, two Medicine 1998;7;197-250.

37. Magnn EF, Antenatal testing among 1001 patients at high risk in the role of ultrasonographic estimation of amniotic Volume. Am 1 obstetgynecol 1999,180,1330-1336.

38. Zhang J, Troendle J, Melkles, klebanolf MA Rayburn WF. Isolated oligohydramnios is not associated with adverse peritoneal outcome B J OG 2004;111:220-225.

Original Article

Outcome of Canal Wall Down Mastoidectomy: A Prospective Clinical Study

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ABSTRACT

Background: *Management of the mastoid in cases of chronic otitis media with cholesteatoma remains challenging. Whether to leave the canal wall up or perform a canal wall down technique continues to be addressed.*

Objective: *To find out the outcome of canal wall down mastoidectomy.*

Methods: *A prospective clinical study was conducted in Department of ENT and Head Neck Surgery, Dhaka Medical College Hospital (DMCH),Bangladesh over a period of six months from 1st January 2016 to 30th June 2016.Fifty patients undergoing canal wall down mastoidectomy of either sex in the age group 5- 60 years were selected.Pre and post operative hearing assessment were done with Pure Tone Audiometry (PTA). Post operative complications of canal wall down mastoidectomy were noted. Post mastoidectomy cavities were examined. All the information were recorded in the fixed protocol.*

Results: *Among 50 cases, age of the patients ranged from 5 years to 60 years with the highest number of cases belonged 2nd and 3rd decade (40% & 30 % respectively) of life ,poor class people group 38 (76%), rural 40 (80%), illiterate and primary education group 40 (80%), farmer 14 (28%) or labourer 13 (26%) or their dependant were sufferer more.Commonest presenting complaint was foul smelling ear discharge with impaired hearing. Isolated cholesteatoma was found in 25(50%) cases, isolated granulation tissues were found in 2 (4%) cases and both cholesteatoma and granulation tissues were found in 23 (46%) cases. An attempt has also been made to detect the specific major complications following surgery (MRM). In our study 8 (16%) patients developed weeping mastoid cavity, 2 (4%) patients developed meningitis, 4 (8%) patients developed meatal stenosis and 1 (2%) patient developed labyrinthine fistula.Pre- operative mean Air-Bone gap was 39.7 dB and post-operative mean Air-Bone gap was 28.8 dB . Mean hearing improvement was 10.9 dB. Hearing was improved in 19 (47.5%) cases , unaltered in 13 (32.5%) cases and deteriorated in 8 (20%) cases. Following canal wall down mastoidectomy after 12th week post operatively out of 50 patients, mastoid cavity was dry in 74% patients and wet in 8 (16%) patients. And among them, 4 (8%) patients had inadequate meatotomy and meatoplasty, 6 (12%) patients had high facial ridge and 4 (8%) patients had large cavity. Residual diseases were detected in 2 (4%) patients.*

Conclusion: *Canal wall down mastoidectomy is a standard treatment modality for the management of CSOM with cholesteatoma. Early diagnosis and timely intervention in skilled hand is prerequisite for better outcome in terms of improved hearing and dry post mastoidectomy cavity.*

Keywords: *Chronic otitis media, Cholesteatoma,Canal wall mastoidectomy.*

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Introduction

CSOM is a common condition worldwide. It is more common in developing countries , like Bangladesh[1,2]. It is an important and relatively common disease that may have serious consequences. It is estimated that over 20 million people worldwide are affected. Of these, one fourth (about 5 million) have cholesteatoma[3] .So, one of the major causes of chronic otitis media is acquired cholesteatoma. Though cholesteatoma is a benign disease histologically, but it's behaviour may be aggressive locally and it's invasive property are associated with significant morbidity and occasional mortality[2].Despite an overall decline in the incidence of otitis media, severe complications still exist[1]. Cholesteatoma may lead to subsequent bone destruction and other complications such as meningitis, brain abscess, labyrinthitis, and facial nerve paralysis, lateral sinus thrombosis, otitic hydrocephalus[2,4]. The only way to eradicate cholesteatoma is via surgery, the aims of which are to achieve a dry self- cleansing ear and completely eradicate the disease[5,6,7]. There are two common surgical approaches in managing CSOM with or without cholesteatoma and chronic mastoiditis, which are canal wall up mastoidectomy and canal wall down mastoidectomy[8,9,10]. In canal wall up mastoidectomy, removal of middle ear and mastoid disease is performed with preservation of the posterior canal wall. Modified radical mastoidectomy (MRM) is

one form of canal wall down mastoidectomy. In MRM, the posterior canal wall is taken down till the level of the facial nerve and the floor of the mastoid cavity is continuous with the floor of the external auditory canal. At the end of operation , the mastoid cavity epitympanum and external auditory canal are converted into a common cavity. Canal wall up mastoidectomy is indicated in limited attico antral disease with minimal hearing loss, intact ossicular chain and well pneumatized mastoid. Apart from this, patient with good compliance for follow up or in paediatrics patient are also suitable for canal wall up mastoidectomy. On the other hand , relative indication for canal wall down mastoidectomy are patient with extensive disease (cholesteatoma or mastoiditis), poor hearing status, poor pneumatized mastoid , and these cases with presence of otogenic complications, failed canal wallup mastoidectomy[8]. Generally hearing results of canal wall up mastoidectomy are better but rates of residual and recurrent disease are more or worser than those of canal wall dowm mastoidectomy[8,9]. The objective of this study was to evaluate outcome or follow-up results of the canal wall down (CWD) mastoidectomy technique for patients with Chronic active otitis media with or without cholesteatoma and chronic mastoiditis for assessing ear dryness, and improving hearing and the recurrence rate[2,8].

Patients and Methods

A prospective clinical study was conducted in Department of ENT and Head Neck Surgery, Dhaka Medical College Hospital (DMCH),Bangladesh over a period of six months from 1st January 2016 to 3oth June 2016. Fifty patients undergoing canal wall down mastoidectomy of either sex in the age group 5- 60 years were selected. Pre and post operative hearing assessment were done with Pure Tone Audiometry (PTA). Post operative complications of canal wall down mastoidectomy were noted. Post mastoidectomy cavities were examined. All the information were recorded in the fixed protocol.

Inclusion criteria were patients between 5-60 years of age with persistent ear discharge with cholesteatoma and patients age<5 years and > 60 years,revision cases and patient with multiple comorbidities, e.g. DM, ill health, post chemo radiation state were excluded

Statistical analysis: After collection, data editing and clearing was be done manually and prepared for data entry and analysis by using SPSS (version-19)

Results

Table- I: Age group distribution of the patients (n=50)

Age(in years)	Number of cases	Percentage (%)
5-10	7	14
11-20	20	40
21-30	15	30
31-40	5	10
41-50	2	4
>50	1	2
Total	50	100%

Table-I shows maximum vulnerable patient was between 11-20 years age group (40%) .

Table-II: Sex distribution of patients (n=50)

Sex	Number of patients	Percentage
Male	30	60
Female	20	40
Total	50	100

Table-II shows that 60 % were male and 40% were female. Male-female ratio was 3:2.

Table-III: Socio-economic condition (n=50)

Socio-economic condition	Number of patients	Percentage
Poor	38	76
Middle class	10	20
Affluent	2	4

Table-III shows that the people of poor socio-economic group were affected more than others.

Table-IV:Residential distribution (n=50)

Resident	Number of patients	Percentage
Rural	40	80
Urban	10	20

Table-IV Shows that people of rural area (80%) suffered more than urban area (20%).

Table-V:Educational Status (n=50)

Educational Status	Number of patients	Percentage
Illiterate &primay education	40	80
Secondary education	7	14
Higher Secondary education	2	4
Graduation	1	2
Total	50	100%

Table-V shows people of illiterate and primary education group (80%) were mostly suffered from COM with cholesteatoma than other educational group.

Table-VI: Occupational status of the patients (n=50)

Occupational Status	Number of patients	Percentage
Labourer	13	26
Farmer	14	28
Student	11	22
House wife	5	10
Service	1	2
Business	6	12
Total	50	100%

Table-VI : shows that farmers (28%) and labourers (26%) suffered more than other groups.

Table-VII: Presenting symptoms in patients of CSOM with cholesteatoma (n=50)

Presenting Symptoms	Number of patients	Percentage
Discharge from ear	50	100
Hearing impairment	46	92
Headache	5	10
Facial weakness	3	6
Post auricular abscess	8	16
Total	50	100%

Table-VII shows that all patients had ear discharge and 46 (92%) of them had hearing impairment.

Table-VIII: Site of tympanic membrane perforation(n=50)

Signs	Number of patients	Percentage
Attic perforation	35	70
Postero superior marginal perforation	13	26
Central perforation	2	4

Table- VIII shows 35(70%) patients were presented with attic perforation and 13 (26%) were presented with postro superior marginal perforation.

Table-IX: Distribution of cholesteatoma and granulation tissues among study population (n=50)

Findings	Number of patients	Percentage
Isolated Cholesteatoma	25	50
Isolated Granulation tissues	2	4
Cholesteatoma & Granulation tissues	23	46
Total	50	100%

Table-IX shows isolated cholesteatoma was found in 25 (50%), isolated granulation tissues were found in 2 (4%) cases and both cholesteatoma & granulation tissues were found in 23 (46%) cases.

Table-X: Associated per operative findings (n=50)

Findings	Number of patients	Percentage
Eroded tegmen tympani	8	16
Eroded sigmoid sinus plate	6	12
Dehiscent facial nerve canal	2	4
Labyrinthine fistula	1	2

Table-X shows Tegmen tympani was eroded in 8 (16%)cases, Sigmoid sinus plate was eroded in 6 (12%) cases and facial canal was dehiscent in 2 (4%) cases.

Table-XI: Complications (early) following Canal wall down mastoidectomy (n=50)

Complications	Number of patients	Percentage
Vertigo	12	24
Wound infection	6	12
Haematoma in post auricular region	4	8
Meningitis	2	4
Labyrinthine fistula	1	2
Wound dehiscent	1	2
Facial nerve palsy/ weakness	0	0
Dead ear	0	0
CSF leakage	0	0

Table-XI shows that vertigo was the most common complication (24%) following surgery.

Table-XII: (Late) Complications developed following canal wall down mastoidectomy

Features	Number of patients	Percentage
Weeping mastoid cavity	8	16
Stenosed meatus	2	4
Residual disease	2	4

Table-XII shows 8 (16%) patients developed weeping mastoid cavity, 2 (4%) patients developed stenosed meatus, 2 (4%) patients had residual disease

Table-XIII: Preoperative hearing status (A-B gap)

Hearing status (Hearing loss in dB)	Number of patients	Percentage
26-40	8	16
41-70	32	64
71-90	10	20
Total	50	100

Table –XIII shows pre operative hearing status. In majority patients(32%) A-B gap were between 41-70 dB.

Table-XIV: Postoperative hearing status (A-B gap)

Hearing status (Hearing loss in dB)	Number of patients	Percentage
26-40	10	25
41-70	24	60
71-90	6	15
Total	40	100

Table XIV shows post operative hearing status. In majority patients(60%) A-B gap were between 41-70 dB.

Table-XV: Comparison between pre operative and post operative A-B gap (n=50)

Hearing status (Hearing loss in dB)	Pre operative (patients in number)	Post operative (patients in number)
26-40	8	10
41-70	32	24
71-90	10	6
Total	50	40
Mean ±SD	39.7 dB	28.8 dB

Table XV shows pre operative and post operative air bone gap. Mean air bone gap in pre operative and post operative were 39.7 dB and 28.8 dB respectively.

Table-XVI: Changed hearing status (A-B gap) after 3 months (n=40)

Hearing Status	Number of patients	Percentage
Improved	19	47.5
10-19dB	12	30
20-29dB	5	12.5
>29dB	2	5
Unchanged	13	32.5
Deteriorated	8	20
Total	40	100%

Table-XVII shows that hearing status improved in 47.5% cases.

Table-XVII: Hearing improvement after 3 months of operation (n=40)

Pre operative Air Bone (A-B) Gap Mean (dB)	Post operative Air Bone (A-B) Gap Mean (dB)	Hearing improvement/ Closure of A-B Gap Mean (dB)
AB Gap= 39.7 dB	AB Gap= 28.8 dB	10.9 dB

Table-XVII shows that Mean closure of A-B gap is 10.9 dB (following surgery).

Table-XIII: Outcome of canal wall down mastoidectomy (12 weeks post operatively)

Observation			Number of patients	Individual %	Total %
Cavities	Dry	Always	24	48	74
		Usual	13	26	
	Wet-	Mucoid	5	10	16
		Mucopurulent	3	6	
	Unknown		5	10	10
High facial ridge			6	12	12
Large cavity			4	8	8
zStenosis of meatotomy and meatoplasty			4	8	8
Residual disease			2	4	4
Meningitis			2	4	4
Labyrinthine fistula			1	2	2
CSF leakage			0	0	0
Dead ear			0	0	0
Facial nerve palsy			0	0	0

Table-XVIII: shows dry cavity in 37(74 %)cases, wet cavity in 8 (16%)cases, unknown in 5 (10%) cases, high facial ridge in 5 (10%) cases and large cavity in 4 (8%) cases, stenosis of meatotomy and meatoplasty in 4 (8%) cases and residual disease in 2 (4%) cases, meningitis in 2(4%) cases.

Discussion

Outcome of 50 cases following canal wall down mastoidectomy in cases of CSOM with cholesteatoma &/or granulation tissue were studied.

CSOM with cholesteatoma is more common among younger age group.The younger age group suffer more as because of cellular mastoid, horizontal position of Eustachian tube and enlarged adenoid. In my study, most of the cases also found were of younger age group (11-20 years) which correlate with above studies. In the present study, table-I showed that the highest number of cases belonged to the 11-20 years age group (40%). The lowest and highest age of the patient was 4 years and 52 years respectively in this series. The majority was young adult in their 2nd decade 40%, 1st decade 14%, 3rd decade 30% ,4th decade 10%, which almost supported by Hossain et al, Fakir et al[11,12]. According to Kangsnaraks et al, Podoshin et al majority of the study population was in their 3rd decade[13,14].

Table II showed that Male-female ratio was 3:2 which mimics the finding of Podoshin et al, Kangsanaraks et al, Mawson[13,14]. But this is not supported by Dawes PJD 65 (where female 77 and male 68 out of 145 patients). In different studies, it was shown that CSOM affected more male than female[2,11,12,16,17]. This might be due to increase prevalence of CSOM among the male or it might be simple reflection of overall high male attendance in hospital. Female are also reluctant or neglected to come forward for treatment in our country.

There is a close correlation between CSOM and poverty[12]. It was not known why this was the cause,but almost certainly it is related to overcrowding, poor hygiene, poor sanitation, malnutrition[2,12,17,18]. Table III showed that poor class patient have a higher incidence (76%).

Table IV Showed that rural people were affected more than urban people[37,38,39,40,41,48,49]. This is similar to the study of Kamal, Biswas, Datta, Joarder, Siddique, Hossain, Fakir et al. But this is contradictory to the study of Podoshin, Browning GG. This contradictory result can be explained by the fact that the Podoshin ,Browning's study was done where poor class people live mostly in overcrowded urban area in developed country[14].

About education status (Table V), maximum patients had low education and primary education group 40 patients (80%). This reflects the higher incidence of cholestetoma in illiterate and with primary education people[11,12].

Again occupation is another factor, which is related to the education, the occupational status of illiterate and primary education group are farmer or his dependent[11,12,19]. Table VI showed that farmer or his dependent (28%) ,labourer or his dependant (26%) suffered more than other occupation group. This reflects the fact that those people are more effected who have lack of health education and are maltreated.

In our study, rural people, illiterate people, farmer & other day labourers were affected by CSOM with cholesteatoma which correlate with above mentioned studies[11,22].

The common clinical symptoms in CSOM with cholesteatoma are malodorous scanty , occasionally blood stained discharge and impairment of hearing[17,24,25,26,27]. In our study malodorous discharge and impairment of hearing were found in all cases which correlated withthe study of Chowdhury, Abdullah , Levensenm, Datta, Marco-Algarra et al . Other variable symptoms which included otalgia, headache, fever, painful swelling behind the ear, facial weakness, vertigo[11,17]. In my study the above mentioned symptoms are variable in frequency and intensity which consistent with the studies of Chowdhury and Hossain et al (Table- VII).

The common clinical signs in CSOM with cholesteatoma are foul smelling scanty , occasionally blood stained discharge with attic or marginal perforation in almost all cases[11,16,17] attic perforation in 70% cases ,marginal perforation in 26% cases and central perforation in 4% cases (Table-VIII), which also correlated with the studies of Akhter, Chowdhury, Hossain et al. The findings of perforation in ear drum were a bit higher than that of Edelstein et al who found more retracted pocket than ear drum perforation. This may be due to late presentation of patients in our country due to ignorance and lack of knowledge of primary health care.

Table-IX showed that isolated cholesteatoma was found in 25 (50%), isolated granulation tissues were found in 2 (4%) cases and both cholesteatoma & granulation tissues were found in 23 (46%) cases.

Table-X showed that tegmen tympani was eroded in 8 (16%)cases, Sigmoid sinus plate was eroded in 6 (12%) cases and

facial canal was dehiscent in 2 (4%) cases.

Table XI- Showed that vertigo was the most common complication in the first post operative day, 12(24%) cases developed vertigo, 6 (12%) cases developed wound infection, 4 (8%) cases developed hematoma in post auricular region, 2(4%) cases developed meningitis, 1(2%) case developed wound dehiscence and 1(2%) case developed labyrinthine fistula. Aural discharge is a common problem in case of open cavity mastoidectomy.

In this study, following surgery, 12(24%) patients reported vertigo or imbalance, which mimic the study of Dawes[15]. According to the history taking, no patient had vertigo before surgery. Ludman28showed that vertigo and imbalance may develop for many reasons after mastoid surgery. Analyses of an individual problem are greatly helped by access to reliable information about the state of the ear before operation, the finding during operation and subsequent progress. It may be due to careless handling close to the stapes foot plate for use of suction , drilling close to the lateral semicircular canal without adequate cooling; unless a suppurative labyrinthitis has been induced by surgery the vertigo soon settles.

In this series, Table XI showed 6(12%) patients developed infection which was slightly higher than Dawes et al (6%). It may be added here that the occurrence of infection also depends upon the patient's personal hygiene, health education, socioeconomic status, otologic history and regular follow up. In this series in every case peri-operative antibiotics were given. John et al (1988) and Hester (1998) did not recommend antibiotic prophylaxis. The later stress the importance of aseptic technique and meticulous attention to surgical detail as paramount to the prevention of complications. This reflects the finding of Palva et al[29] (1976) that specific instruction of the residents regarding surgical technique prevented the occurrence of wound infection.)

Aural toileting with unsterile cotton is another factor for infection and aural discharge.

Table XIIIalso showed that 6 patients (12%) had high facial ridge and 4 patients (8%) had large cavities. Sade et al[30] have identified four factors which determined a dry cavity post operatively- 1. small and medium sized cavity, 2. low facial ridge, 3. large meatal opening, 4. Presence of air in the middle ear. Rambo concluded that retained infected mucosa in the mastoid bowl predisposes to a discharging cavity[31].

Dead ear may be consequence of mastoid surgery. Harkness reported 7 cases of dead ear in their 365 open cavity surgery at the Royal College of surgeons of England (1.9%). In this study no dead ear is found. The explanation may be like that in Harkness had included radical mastoidectomy procedure in open cavity surgery[32]. Radical mastoidectomy is the main cause of dead ear. Certain surgical precautions are advocated such as disarticulation of the incus before cleaning of attic, dissection of the malleus in the direction of the handle and conservative removal of granulation tissue around the stapes[29]. On the other hand, we used drill machine during surgery. Arie Man suggested that there is no damage exclusively due to the drill noise during mastoid surgery[33].

Probably the most feared complication of middle ear surgery is facial nerve injury and the small sample has fortuitously avoided this feared complication. The Royal College of surgeons mastoidectomy audit (Harkness et al 1995) 57 estimated (0.8%) patient developed this feared complication and Wormwald, Nelssen (1997) reported a 1.7% incidence of facial nerve palsy following mastoid surgery. But they did not mention that this incidence was due to very extensive disease or due to extensive surgery –radical mastoidectomy.

Douglas Geen stated that facial nerve monitor will undoubtedly play an important role in ear surgery for resident and occasional otologist. In our series we did not use nerve monitor.

In our series 2 patients (4%) developed intracranial complication- meningitis (table XIV). Though intracranial complications are rare34, we used peri-operative and post operative antibiotic for 10 days (atleast). Meningitis is a rare complication of canal wall down mastoidectomy. Beeden et al 1969 also described 3 cases of meningitis and 2 cases of subdural abscess developed following mastoid surgery. There are reports of nominal aphasia attributed to cortical venous sinus thrombosis (Beeden et al 1969; Girgri and Siegler, 1985; Osammor and Baruah, 1989).

Table XII showed that 4(8%) patients developed stenosed meatus, which is similar to Singha[35] (6%). Lee and Schuknecht (1971) recorded 34 stenosis in that series of 1074 patients. Shaam et al (1995) recorded 2 cases out of 37, both required meatotomy and meatoplasty to improve the migration of keratin.

In this series, it is seen, except meningitis and labyrinthine fistula, no other important complication, like facial nerve palsy, dead ear, CSF leakage was developed. Though it is a series of small number of patients (n=50). In early post operative follow up minor complications like vertigo, infection all are subsided within 6-12 weeks post operatively. In our series total 8 (16%) patients developed complications; all of them developed aural discharge.So, ear discharge was still a problem , known as 'cavity problem' following surgery.

It should be mentioned here that 10% patients (n=5 out of 50) were lost from follow-up. This is a common problem in our country and we believe that if a patient is going to be lost from follow-up , the patient is free from disease problem.

The pre-operative Air conduction was 30- 60 dB, mean 45 dB and bone conduction was 10-30 dB, mean 20.7 dB, pre-operative air bone gap was 10-40 dB, mean 24.29 dB in the study of Lasisi et al[36] . In our study, pre-operative air conduction was 35-75 dB, mean 59.6 dB and bone conduction was 10-35 dB, mean 19.9 dB, air-bone gap 39.7 dB . This result is almost similar to above mentioned study.

Table XIII showed pre operative hearing status . In majority patients(32%) A-B gap were between 41-70 dB. In the study of Lasisi et al Post-operative air conduction was 25-55 dB, mean 39.29 dB, the bone conduction was 15-35 dB, mean 20.23 dB, post-operative air bone gap 10-35 dB, mean 19.29 dB. In our study air conduction was 48.5 dB, bone conduction was 19.7 dB, and air bone gap was 28.8 dB, which also correlates with above mentioned study.

Table XIV showed post operative hearing status. In majority patients (60%) A-B gap were between 41-70dB.

It was showed in one study that after surgery hearing was better than 40 dB in 42% patients, between 40-60dB in 39% and deteriorated in 4% patients[2]. In another study, hearing improved in 30% cases, remained unchanged in 55% cases, and worsened in 15% cases following surgery. The mean hearing gain was only 5 dB[37].

In our study, hearing was improved by 10-19 dB in 30% cases , 20-29 dB in 12.5% cases, and more than 29 dB in 5% cases. Thus hearing threshold was improved in 47.5% cases, unchanged in 32.5% cases and deteriorated in 20% cases(Table- XVI) . These results are more or less similar to above mentioned two studies .

In a study, canal wall down mastoidectomy and Wullstein Type III Tympanoplasty was done in 21 cases of CSOM with ossicular erosion resulting the main hearing gain was 5 dB[36]. In our study results of 50 cases of canal wall down mastoidectomy with Type III Tympanoplasty in CSOM with cholesteatoma with almost similar result (10.9 dB) of above study (Table-XVII).

On examination of post mastoidectomy cavities (n=50) those patients had discharging ear (n=8) whose all cavity were not healed completely (Table-XVIII). Out of them 4(8%) patients had inadequate meatotomy and meatoplasty, 6(12%) patients had high facial ridge, 4(8%)patients had large cavities. 2(4%) patients had residual disease (but no recurrence, as recurrence of disease takes time atleast 6 months). So it can be said in our series, only major problem is 'cavity problem'.

Sade et al[30] have identified four factors which determined a dry cavity post operatively- 1. small and medium sized cavity, 2. low facial ridge, 3. large meatal opening, 4. Presence of air in the middle ear. Rambo concluded that retained infected mucosa in the mastoid bowl predisposes to a discharging cavity[31].

Table XVIII Showed that after 12th week post operatively, 74% cavities were dry, 16% cavities were wet, which are almost supported by Harkness (60% were dry)[19]; Brain JG (wet cavity 30%).

When patient presented with CSOM with cholesteatoma without complication though there are many types of operation – atticotomy, obliteration procedure, radical mastoidectomy, modified radical mastoidectomy with tympanoplasty ; primarily simple modified radical mastoidectomy was acceptable operative procedure. Harkness[32] showed 80% of mastoidectomies performed were open cavity procedures; Jacobe Sade[30] showed out of 368, 200 were open cavity procedure. The complication and outcome depend on the extension of disease process, experience of the surgeon and ventilatory system of the ear.

Conclusion:

The prevalence of CSOM with cholesteatoma is still high in rural people of younger age group in low socio economic class. Lack of awareness about the nature, complication and consequence of disease, inadequate facilities in illiterate and under educated population lead to grave complications. In this study an attempt has been made to detect the specific complication, condition of post mastoidectomy cavity, the status of the meatotomy and meatoplasty, incidence of residual or recurrence of the disease and post operative hearing status following canal wall down mastoidectomy. The potential complications of this type of surgery are discussed, as are measures that can be taken to reduce the risk of post operative complications. Recognizing the limitation of the study, our experience is that, if early diagnosis and timely intervention – i.e. canal wall down mastoidectomy (mainly modified radical mastoidectomy) is done meticulously , post operative care and follow up is maintained properly ,morbidity as well as mortality will be lessened, hearing will be improved and complication will be minimized

3.11 References:

1. Garap J P, Dubey SP. Canal wall down mastoidectomy:Experience in 81 cases. Otology & neurotology 2001; vol.22:451-456

2. Ajalloueyan M. Experience with surgical management of cholesteatomas.ArchOtolaryngol Head Neck Surgery2006; Vol.132:931-933

3. Aquino JEAP, Filho NAC, Aquino JNP. Epidemiology of middle ear and mastoid cholesteatomas. Study of 1146 cases. Braz J Otorhinolaryngol 2011; Vol.77:341-47

4.Kos MI, Castrillon R, Montandon P, Guyot JP. Anatomic functional long term results of canal wall down mastoidectomy. Ann OtolRhinol LaryngoL2004; 113 (11): 872-876.

5. Ajalloueyan M. Modified radical mastoidectomy :Techniques to decrease failure. Medical journal of the Islamic Republic of Iran 1999; Vol.13:179-183

6. Chan CY, Chan YM. Mastoid obliteration and reconstruction: A review of techniques and results. Proceeding of Singapore Healthcare 2012; Vol.21:23-29

7. Sergi B, Gali J, Battista M, Corso ED, PaludettiG.Dealing with paediatriccholesteatoma:how we changed our management. ACTA Otorhinolaryngol 2014; Vol.34:138-143.

8. Abdullah AB, Hashim SM, Awang MA, Saim L. Outcome of canal wall down mastoidectomy: Experience in sixty three cases. Med J Malaysia 2013; vol.68:217-2213. Parvin N. Hearing outcome in canal wall down mastoidectomy with Type 3 Tympanoplasty. State journal of Otolaryngology:21-23

9. Browning GG et al. Chronic otitis media. In: Gleeson M et al. Scott Brown's Otorhinolaryngology, Head & Neck Surgery. 7th ed. London, Hodder Arnold.2008: 3396-3445

10. Goh BS, Teoh JW, Faizah R, Lokman S, Asma A. Paediatric cholesteatoma: Experience of University Kebangsaan Malaysia Medical Centre. BruneiInt Med J 2012; Vol.8:71-77

11. Hossain MM, KunduSC, Hoque MR, Shamsuzzaman AKM, Khan m k Halder KK. Extracranial complicatios of chronic suppurative otitis media. A study on 100 cases. Mymensingh Medical Journal, 2006, Jan 15: 4-9.

12. Fakir MAY, Hanif A, Ahmed KU & Haroon AA. Intracranial complications of CSOM- A study of 40 cases. Bangladesh J of otorhinolaryngology

13. Kangsanarak J, et al. 1993. Extracranial and intracranial complications of suppurative Otitis Media- reportd of 102 cases Thailand. The journal of laryngology and otology, Vol 107, 999-1004

14. Podoshin L, 193. Cholesteatoma on epidemiological study, Ann otol.197: 100-104.

15. Dawes PJD, 1999. Early complications of surgery for chroic otitis media, The journal of laryngology and otology, Vol 113, 803-810.

16. Aktar N, Alauddin M, Siddiquee BH, Alam MM & Ahmed MU. Hearing loss in Chronic suppurative otitis media, Bangladesh J of otorhinolaryngology, 2003;9 (1/2): 19-23.

17. Chowdhury MA, Alauddin M, 2002. Comparative study

between tubotympanic and attico antral types of CSOM. Bangladesh Med. Res. Counc. Bull, 28 (1),36-44.

18. Sergi B, Gali J, Battista M, Corso ED, PaludettiG.Dealing with paediatriccholesteatoma:how we changed our management. ACTA Otorhinolaryngol 2014; Vol.34:138-143.

19. Kamal N, Joarder AH, Chowdhury AA, Khan AW, 2004. Prevalence of chronic suppurative otitis media among the children living in two selected slums of Dhaka city. Bangladeshmed.Rec. Counc. Bul, 30(3), 95-104.

20. Biswas AC, Joarder AH, Siddiquee BH, 2005. Prevalence of CSOM among rural school going children. Mymensingh Med J. Jul;14 (2): 152-5.

21. Datta PG, Alauddin M, FirojAK, Zahurul AHM, 2005. A comparative study of prevalence of CSOM between rural and urban school going children. Bangladesh Journal of otolaryngology, 11(1/2), 17-21.

22. Joarder AH, Manjur M, Taous A, Hossen D, 2006. Prevalence of CSOM in selected rural and uban community of Bangladesh. Bangladesh J of otorhinolaryngology, 12(1), 1-6.

23. Siddique BH, Khan AH. Chronic suppurative otitis media – A rural area based study. SirSalimullahMedicalCollege Journal, 1995; 3 (1):12-16.

24. Abdullah A, Hashim SM, Awang MA, Saim L. Outcome of canal wall down mastoidectomy: Excperience in sixty three cases, Med J Malaysia 2013; 68(3): 217-21

25. Levensenm. Management of congenital pediatric cholesteatomas. American Journal of Otology. 1999; 10:121-123.

26. Marco- Algarra J et al, Cholesteatoma in children: results in open versus closed techniques; the Journal of Laryngology and Otology, Oct.19921; (105): 820-824.

27. Datta PG, Newton VE, AminMN, 1995. Chronic suppurative otitis media - A major cause of hearing impairment in developing countries. J Bangladesh Coll Phys Surg. Vol.13, 24-27.

28. Ludman H. Complications of suppurative otitis media – In: Booth JB, editor Scott- Brown's oto laryngology. 6 th ed. Vol-3. London: Butterworth- Heinman, 1997: 3/12/ 12-27.

29. Palva T, Johani, Palva A, 1973. High tone sensorineural losses following chronic ear surgery, Arch Otolaryngol, Vol 98, 176-179.

30. Sade J et al, 1982. The Mersupialized radical mastoid. J LaryngolOtol, 96, 869-875.

31. Rambo IHT, 1979. Mastoid surgery, Effect of retained mucosa on healing, Ann of Oto- Rhino- Laryngo, 88, 701-707.

32. Harkness P, Brown P, Fowler S, Grant H, Ryan R & To Pham J. Mastoidectomy audit: results of the Royal College of Surgeons of England comparative audit of ENT Surgery, Clin. Oto Laryngol, 1995; 20, 89-94

33. Man A, Winer M, 1985. Does drill noise during mastoid surgery affect the contralateral ear, the American Journal of Otology, Vol 6, 2-3.

34. Alauddin M, Manjurul M, Akaiduzzaman DGM, 2006. Complications of mastoidectomy. Bangladesh journal of otol, 12 (1),7-11.

35. Singha NK, 1997. Complications of mastoidectomy. BangladeshCollege of Physicians and Surgeons.

36. Lasisi, A Keem O. Hearing outcome after canal wall down mastoidectomy and wullstein type iii tympanoplasty: East and cental African Journal of surgery, 2007; 12 (12) : 44-47.

37. Vartiainen E &Vartiainen J. Hearing results of surgery for acquired cholesteatoma. Ear Nose Throat J. 1995 mar; 74 (3); 160-164.

Original Article

The Association Between Inter-pregnancy Interval (IPI) And Pregnancy Outcome

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ABSTRACT

Inter-pregnancy interval (IPI)is the time elapsed between the women's last delivery and the date of the last menstrual period for the index pregnancy expressed in completed months.

The effect of IPI on maternal morbidity and mortality (i.e. maternal death, pre-eclampsia, eclampsia, gestational diabetes mellitus, third trimester bleeding and premature rupture of membranes, postpartum haemorrhage, and puerperal sepsis) has received less attention. Birth spacing may also affects pregnancy outcome, such as whether the pregnancy results in a live birth, stillbirth, miscarriage, or induced abortion.

Whether IPI is an independent risk factor or whether the association is due merely to confounding by other factors (such as maternal age, socioeconomic status, and reproductive history) is unclear. Data were collected by direct interview & reviewing records using a structured data collection sheet about pregnancy, maternal & perinatal outcome among 661 parous women admitted in the department of obstetrics &gynaecology in Shaheed SuhrawardyMedical College Hospital Dhaka during 1st April to 30th December 2009. The aim of this study is to evaluate the association between inter-pregnancy interval & pregnancy outcomes. It was proved that both short & long inter-pregnancy intervals have been found to increase the risk of various adverse perinatal & obstetric outcomes.

Keywords: *Birth spacing, short & long inter pregnancy interval.*

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Introduction

The time interval between one pregnancy and the next may affect the risk of pregnancy complications. Both short and long interpregnancy intervals have been associated with adverse outcome, but the bulk of adverse effects have been associated with short intervals[1-3]. Whether the interpregnancy interval is a significant independent biological risk factor for adverse pregnancy events is important because women have some control over the spacing of their pregnancies and thus could potentially reduce their risk of adverse outcomes. Avoidance of short intervals can be achieved through postpartum provision of contraception, but avoidance of long interpregnancy intervals is more problematic since a desired pregnancy may be precluded by subfertility, availability of a partner, economic issues, or illness[4].

There are many reasons for the associations described in this topic, and causality should not be assumed. Some examples:

• If the interval between births is measured and the second birth is preterm, the interbirth interval will be shorter than for a term birth and associated with higher neonatal mortality due to prematurity[5].

• After a stillbirth or neonatal death, women often wish to conceive again with minimal delay. If the causative factors for the fetal or neonatal death recur, an association between short interpregnancy interval and perinatal mortality would be observed.

Breastfeeding both improves infant survival and lengthens the interval between pregnancies due to lactational amenorrhea, thus confounding the relationship between longer interpregnancy interval and improved pregnancy outcome.However, breastfeeding may also deplete the mother, thereby worsening pregnancy outcome.

Materials & methods

A cross-sectional study was done among 661 parous women admitted in the Department of Obstetrics &Gynaecology, in a tertiary level hospital (Shaheed Suhrawardy Medical College Hospital) Dhaka. during 1st April to 30th December' 09. Parous women with known medical disorder were excluded. Data were collected by direct interview and reviewing records using a structured data collection sheet about pregnancy, maternal and perinatal outcome. In this study IPI of 24-60 months was taken as the reference category. Data analysis was performed using SPSS version-16 and statistical analysis was done using appropriate statistical test (Odds ratio = 95% CI, Chi square test (c2) and fisher exact test, results considered significant when $P<0.05$.

Results

Spontaneous abortion was higher ($p<0.001$) in 6 -11 months and 12 – 24 months IPI, (OR: 3.00: 95% CI 1.61 - 5.58 and OR: 2.29: 95% CI 1.19 - 4.41 respectively). Induced abortion was higher ($p<0.001$) in 12 – 24 months IPI, (OR: 3.47: 95% CI 1.71 - 7.08). Maximum IUD was found in <6 months of IPI. IPI <24 months increased ($p<0.05$) the risk of PROM, oligohydramnios, preeclampsia, IUGR (majority are< 6 months). PE, PROM was found more in >60 months IPI. IPI <6 months had increased ($p<0.05$) the risk of Preterm birth, Neonatal sepsis and LBW.

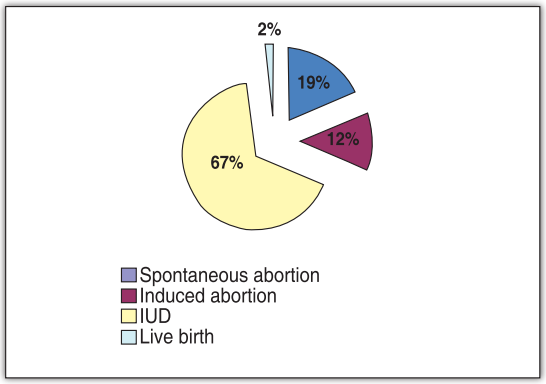

Fig 1: Distribution of total study population according to outcome of pregnancies irrespective of IPI.

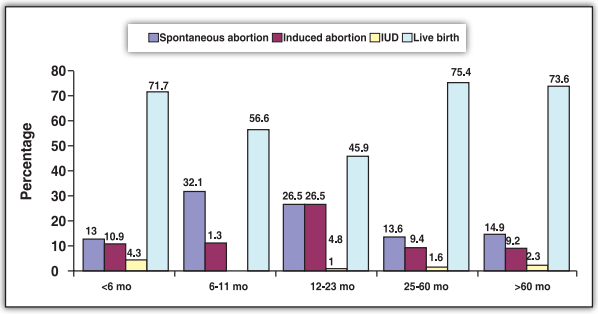

Fig 2: Distribution (percentage) of the pregnancy outcomes according to length of IPI

	< 6 mo (n=66)		6-11 mo (n=60)		12-23 mo (n=45)		> 60 mo (128)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PROM	7.90	(3.76-16.79)*	5.73	(2.67-12.40)*	5.12	(2.21-11.89)	1.45	(0.70-3.01)
PIH	0.57	(0.22-1.42)	1.51	(0.70-3.22)	0.64	(0.22-1.77)	0.68	(0.34-1.35)
Oligohydramnios	4.13	(1.73-9.93)*	1.22	(0.39-3.74)	1.38	(0.39-4.55)	0.64	(0.22-1.81)
APH	0.71	(0.15-3.01)	1.36	(0.38-4.72)	1.46	(0.36-5.58)	0.48	(0.12-1.78)
Preeclampsia	5.58	(1.24-28.30)*	3.36	(0.61-19.63)	1.07	(0.19-5.58)	2.31	(0.50-11.94)
IUGR	6.48	(1.49-32.09)*	3.36	(0.61-19.63)	2.19	(0.25-16.80)	1.52	(0.28-8.72)
Hydramnios	2.24	(0.35-14.36)	4.27	(0.85-23.48)*	2.19	(0.25-16.80)	0.75	(0.09-5.59)
GDM	1.32	(0.24-6.62)	0.00	(0.00-2.7)	2.71	(0.58-12.37)	0.44	(0.06-2.62)

Table1: Odds ratio (95% confidence interval) for adverse maternal outcomes according to inter-pregnancy interval (IPI)

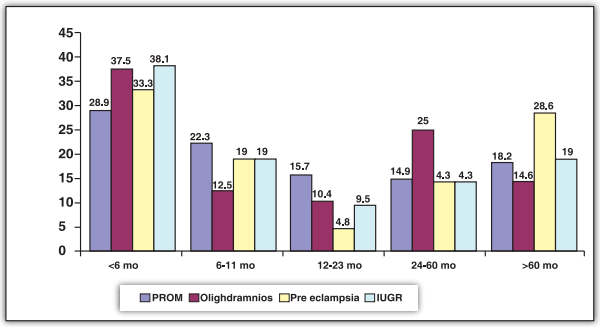

Fig 3: Occurrence of PROM, Oligohydramnios and Pre-eclampsia in different inter-pregnancy interval

Perinatal Outcome	< 6 mo (n=66)		6-11 mo (n=60)		12-23 mo (n=45)		> 60 mo (128)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Preterm birth	13.14	(4.69-38.7*)	2.09	(0.53-8.16)	3.0	(0.75-11.8)	2.4	(0.8-7.37)
Neonatal sepsis	11.21	(2.16-77.7*)	9.38	(1.71-67.6*)	8.88	(1.45-68.9*)	3.49	(0.62-25.5)
Neonatal jaundice	1.40	(0.57-2.09)	0.92	(0.33-2.52)	1.75	(0.66-4.6)	0.72	(0.31-1.67)
SGA	6.48	(1.49-32.09)	3.36	(0.61-19.6)	2.19	(0.25-16.8)	1.52	(0.28-8.72)
LBW (due to prematurity+SGA)	19.25	(6.47-61.4*)	3.67	(0.99-14.1*)	1.99	(0.36-10.1)	3.41	(1.11-1.22*)

Table 2: Odds ratio (95% confidence interval) for Perinatal outcome among the live birth according to inter-pregnancy interval (IPI) (n=443)

Discussion

A total of 661 patients ranging from 18 to 45 years pregnant woman were included in the study, in the Department of Obstetrics & Gynaecology, Shaheed Suhrawardy Medical College Hospital, Dhaka during April to 30th December'09.

This cross-sectional study was carried out with an aim to find out the relationship between the inter-pregnancy intervals with pregnancy outcome.The present study findings were discussed and compared with previously published relevant studies.

In this current study it was observed that majority of the patients belongs to of 20-34 years age group in all five age groups of inter-pregnancy interval. Regarding the level of education most (44.9%) of the patients has completed the secondary education and nearly one fourth (24.4%) of patients were illiterate. More than ninety percent of the patients were housewife and most of them came from middle socio-economic condition. Only 122(16.9%) received regular antenatal checkup, 206(31.2%) didn't received any antenatal checkup and more than a half (51.9%) of the patients received irregular antenatal checkup during their pregnancy period.

CondeAgudelo and Belizánfound in their study that there were no obvious differences among the interpregnancy interval groups with regard to number of previous deliveries, mother's education and prenatal care during pregnancy.

It was observed among study population (661) 124(19.0%) had spontaneous abortion. 82(12.0%) induced abortion, 12(2.0%) IUD and 443(67.0%) had live birth, which also divided into five groups according to their inter-pregnancy interval (IPI). Maximum (191) number of patients were found 25-60 months of inter-pregnancy interval and least number (92) of patients was found <6 months of inter-pregnancy interval. (IPI)

DaVanzo et al. reported that 56.0% of IPIs of <6 months, more than 30% of IPIs of 6–14 months, but just 7.7% of IPIs of 15–26 months and only 2.8% of IPIs of 27–50 months. Compared with IPIs of 27–50 months, IPIs of <6 months are 31 times more likely to begin with a miscarriage, 16 times more likely to begin with a stillbirth, and 6 times more likely to begin with an induced abortion. However in the current study it was observed that 28.3% of IPIs <6 months, 43.4% of IPIs 6-11 months, 54.1% of IPIs 12-24 months, 24.6% of IPIs 25- 60 months, 26.4% of IPIs >60 months.

In this present study it was observed that spontaneous abortion was significantly ($p<0.001$) higher in 6-11 months and 12–24 months inter-pregnancy interval (IPI). Odds ratio: 3.00(95%CI 1.61) for 6-11 months inter-pregnancy interval (IPI) and odds ratio: 2.29(95%CI 5.58) for 12-24 months inter-pregnancy interval (IPI), which indicates that 2 to 3 times increased the spontaneous abortion during 6-11 months and 12–24 months inter-pregnancy interval (IPI). Induced abortion was significantly ($p<0.001$) higher in 12–24 months inter-pregnancy interval (IPI), where odds ratio: 3.47(95% CI 1.71 to7.08), which indicates that almost 3 to 4 times increased the induced abortion during the inter-pregnancy interval (IPI).

In this current study it was observed that PROM, PIH, oligohydramnios and APH were more common obstetric characteristic among the all inter-pregnancy interval(IPI) group, however, pre-eclampsia 7(33.3%) and IUGR 8(38.1%)were found more in <6 months IPI than others IPI groups. Whereas hydramnios was found in 5(33.3%) cases in 6–11 months IPI and GDM in 5(35.7%) cases in 24-60 months IPI. In this study the occurrence of PROM was found to be higher in <6 months and 6-11 months category of IPI; which is another time higher among mothers with IPI >60 months. PIH was found to be higher among longer IPI. Oligohydramnios is also higher among mothers which short IPI (<6 months). Occurrence of PIH was found to be higher in both short (<6 months) and long (>60 months) IPI. IUGR polyhydramnios occurred in higher percentage among, mother with short IPI (<6 month). Occurrence of GDM and eclampsia did not follow any prototype. Conde Agudelo and Belizán (2000) mentioned in their study that women with short interpregnancy intervals had the highest rates of third trimester bleeding, premature rupture of membranes, puerperal endometritis, anaemia, and maternal death. The rates of preeclampsia, eclampsia, and gestational diabetes mellitus were highest among women with intervals longer than 59 months. A slight increase in the rates of third trimester bleeding and maternal death was also seen in women with this interpregnancy interval. The results obtained by the investigator are comparable with the present study.

Compared with the mothers with inter-pregnancy interval 25–60 months in this current series it was observed that, mothers with inter-pregnancy shorter than 6 months had significantly ($p<0.05$) increased the risk of PROM, Oligohydramnios,Pre-eclampsia and IUGR. Mothers with inter-pregnancy interval 6–11 months, had significantly ($p<0.05$) increased the risk of PROM and Hydramnios. Conde Agudelo and Belizán have showed the relation of interpregnancy intervals to adverse maternal outcomes. Compared with mothers with interpregnancy intervals of 18 to 23 months, mothers with intervals shorter than 6 months had about a 70.0% increased risk of third trimester bleeding and premature rupture of membranes and a 30.0% increased risk of anaemia and puerperal endometritis. Moreover, a short interval between pregnancies was associated with a significantly greater risk of maternal death (adjusted odds ratio 2.54; 95% confidence interval 1.22 to 5.38). When interpregnancy intervals were dichotomised to shorter than 6 months versus 6 months or more, women with short intervals between pregnancies were significantly more likely to die than women conceiving at or after 6 months (2.04; 1.13 to 3.78). On the other hand, women with interpregnancy intervals of 60 months or more were 1.8 times more likely than women with intervals of 18 to 23 months to develop preeclampsia and eclampsia. The investigators found no significant differences in the effect of interpregnancy interval on gestational diabetes mellitus, and no relation between the interval and the risk of postpartum haemorrhage, which are analogous with the current study.

In this study it was observed that more than a half (51.5%) to 80.0% of the patients underwent caesarean section in all category of inter-pregnancy interval.

Regarding the postpartum maternal complications, it was observed in this present series that sepsis and PPH were predominant in 24–60 months of inter-pregnancy interval (IPI) and wound infection was found more in > 60 months inter-pregnancy interval (IPI). As a whole sepsis was (11.5%) common-complication; followed by PPH (7.9%) and wound infection (0.9%) among all women 30 gave birth to live birth babies. In addition, none of the postpartum complication were significantly ($p<0.05$) related to inter-pregnancy interval. The results obtained in the present study are consistent with Conde Agudelo and Belizán study.

Regarding perinatal outcome preterm birth were common in all categories (due to prematurity+SGA). Furthermore, mothers with inter-pregnancy shorter than 6 months had significantly ($p<0.05$) increased the risk of Preterm birth, neonatal sepsis and LBW (due to prematurity+SGA) compared with the mothers with inter-pregnancy interval 25-60 months. Mothers with inter-pregnancy interval 6–11 months, had significantly ($p<0.05$) increased the risk of sepsis and LBW (due to prematurity+SGA). Mothers with inter-pregnancy interval 12–23 months, had significantly ($p<0.05$) increased the risk of sepsis and mothers with inter-pregnancy interval 12–23 months, had significantly ($p<0.05$) increased the risk of LBW (due to prematurity+ SGA).

Regarding obstetric outcome in the second birth Smith et al(2003).reported from their univariate analysis that women with a short interpregnancy interval were more likely to have an extremely preterm birth, a moderately preterm birth, or a neonatal death. The strength of these associations was attenuated by adjustment for maternal age, height, socioeconomic deprivation category, previous birth weight vigesimal, and previous caesarean section, but significant associations persisted in multivariate analysis. The adjusted attributable fractions for these associations were 6.1% (95% confidence interval 1.9% to 10.2%) for extremely preterm birth, 3.9% (1.3% to 4.2%) for moderately preterm birth. The excess of preterm second births persisted when the analysis was confined to spontaneous preterm births. An interpregnancy interval of less than six

months was associated with an increased risk (compared with an interpregnancy interval of 18-23 months) of spontaneous preterm birth, both 24-32 weeks (adjusted odds ratio 2.2, 95% confidence interval 1.2 to 4.1) and 33-36 weeks (1.6, 1.2 to 2.2). The associations between interpregnancy interval and unexplained stillbirth were virtually identical when estimated using time to event methods, which are in agreement with the current study.

The reasons for the association between a short interval between pregnancies and adverse maternal out comes are unclear. Most of our findings might be explained by the maternal depletion hypothesis, which suggests that short intervals do not allow the mother to recover from the physiological stresses imposed by the previous pregnancy (Miller 1991, Winkvist A 1997, Khan 1998). This results in depletion of maternal nutrient stores and anaemia, which have been found to play a part in the pathogenesis of premature rupture of membranes and puerperal endometritis(Alger 1986, Libombo 1994). With regard to the increased risk of third trimester bleeding, postulate that a short interval between pregnancies might interfere in normal processes of remodeling of endometrial blood vessels after delivery, with subsequent uteroplacental under perfusion (Naeye R 1983),thereby increasing the likelihood for placental abruption and placenta previa. All the previously mentioned conditions may contribute to the increased risk of maternal death among women with short interpregnancy intervals found in our study. Other alternative explanations for the relation between short interpregnancy intervals and adverse maternal outcomes might be postpartum stress levels, socioeconomic factors other than marital status and education, unstable lifestyles, occupation, community variables (for example, crime, drug misuse, housing), failure to use healthcare services or inadequate use of such services, and other behavioral or psychological determinants.

The reasons for the association between a short interval between pregnancies and adverse perinatal outcomes are unclear. A possible explanation is the maternal nutritional depletion hypothesis (Miller 1991, Winkvist A 1997) which states that a close succession of pregnancies and periods of lactation worsen the mother's nutritional status because there is not adequate time for the mother to recover from the physiological stresses of the preceding pregnancy before she is subjected to the stresses of the next. This results in depletion of maternal nutrient stores, with the subsequent increased risk of adverse perinatal outcomes(Miller 1991). The folate depletion hypothesis claims that maternal serum and erythrocyte concentrations of folate decrease from the fifth month of pregnancy onward and remain low for a fairly long time after delivery. Women who become pregnant before folate restoration is complete have an increased risk of folate insufficiency at the time of conception and during pregnancy. As a consequence, their offspring have higher risks of neural tube defects, intrauterine growth restriction, preterm birth, and LBW (Smits 2001). Some investigators have attributed the higher risk of poor pregnancy outcomes to several factors associated with having short intervals, such as socioeconomic status, unstable lifestyles, failure to use health care services or inadequate use of such services, unplanned pregnancies, and other behavioral or psychological determinants (Erickson 1979, Klebanoff 1999). However, the fact that the birth spacing effects are not strongly attenuated when socioeconomic and maternal characteristics are controlled which suggests that the effects are not caused by these confounding factors. Some hypotheses have also been proposed to explain the relationship between long intervals and adverse perinatal outcomes (Zhu et al 1999)which have hypothesized that, after delivery, a woman's physiologic reproductive capacities gradually decline, becoming similar to those of primigravid women (ie, "the physiological regression hypothesis"). This hypothesis is supported by the observation that perinatal outcomes for infants conceived after an excessively long interpregnancy interval are similar to outcomes of infants born to primigravida women. Another possibility is that unmeasured factors, such as sexually transmitted infections or maternal illnesses, may cause both adverse fertility and pregnancy outcomes. (Zhu BP 1999) These factors could differ for women in developed and developing countries. Finally, residual confounding may still be an explanation for at least part of the reported associations.

Conclusions

In this particular sample, Inter-pregnancy interval (IPI) between 25-60 months have a lower chance of fetal loss and less adverse maternal & perinatal outcome than those with shorter and longer IPIs Providing counseling about the potential negative consequences of short inter pregnancy intervals & improving women's contraceptive use to reduce rates of unintended pregnancy would likely reduce the proportion of short IPI pregnancies.

Recommendation

From the finding of the study it may be recommended thatInter pregnancy interval should be at least 2 years.IPI of 5 years or more also to be discouraged.A larger study with bigger sample size is also being recommended to formulate the maternal standard of IPI.

References:

1. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA 2006; 295:1809.
2. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: a systematic review. Am J ObstetGynecol 2007; 196:297.
3. Conde-Agudelo A, Belizán JM, Norton MH, Rosas-Bermúdez A. Effect of the interpregnancy interval on perinatal outcomes in Latin America. ObstetGynecol 2005; 106:359.
4. Thiel de Bocanegra H, Chang R, Howell M, Darney P. Interpregnancy intervals: impact of postpartum contraceptive effectiveness and coverage. Am J ObstetGynecol 2014; 210:311.e1.
5. Miller JE, Trussell J, Pebley AR, Vaughan B. Birth spacing and child mortality in Bangladesh and the Philippines. Demography 1992; 29:305.
6. Gemmill A, Lindberg LD. Short interpregnancy intervals in the United States. ObstetGynecol 2013; 122:64.

Original Article

Study of Basilar Tip Anatomy in relation to Distal Basilar Artery Disposition and Origin and Distribution of the Perforating Arteries Among Indian Population Using 2D Digital Subtraction Angiography.

Islam MS[1], Husain S[2], Hossain MA[3] ,Khan MAM[4]

ABSTRACT

Background: *The basilar artery is the prominent Median vessels of the vertebrobasilar system and usually terminates in two posterior cerebral arteries. the perforating arteries originate from P1segment, based on how both anterior longitudinal neural arteries merged into a basilar artery in the embryonic period. When merging was symmetrical, whether in the early stages or later, the origins are more or less equally distributed; however, when merging was asymmetrical, the great majority of the perforating arteries stem from the PI segment on the side that merged earliest (cranially).*

Objective: *This observational study was performed to evaluate origin and distribution the perforating branches to the interpeduncular fossa in relation to cranial and caudal fusion of basilar artery disposition.*

Methodology: *We studied origin and distribution of perforating arteries of distal basilar tip in 76 cases retrospectively in July to December 2016 using 2D digital subtraction angiography (SiemensArtis Zee system).*

Result: *Analysis of basilar tip anatomy among the cases showed 78.9% were caudal fusion, where as 21.0% was cranial fusion. Among the caudal fusion group 46.0% was Asymmetrical and 32.8% was symmetrical disposition. Cranial symmetrical fusion was found in 21.0 % cases. Origin of P1 thalamoperforating branches were classified into five different types at the origin of P1 segment:Type I was observed in 38.1% cases, Type II in 27.6% cases, Type III in 17.1% cases,Type IV in 7.8% cases and Tpe V was found in 9.2 cases.*

Conclusion:*The ability to predict the Distal basilar anatomy and origin of perforating branches to the interpeduncular fossa improves the safety of the treatment avoiding the risks of ischemic complications in the diencephalo-mesencephalic region and allowing the P1 segment to be safely sacrificed in certain cerebrovascular diseases and malformation, particularly by aneurysms, arteriovenous malformations(AVMs) and occlusive disease.*

Key words: *basilar tip, perforators, interpeduncular fossa.*

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Introduction

From the embryonic point of view, the internal carotid artery gives off two main branches, the cranial division (future anterior cerebral, anterior choroidal and middle cerebral arteries), and the caudal division, which corresponds to the posterior communicating artery, followed by the P1 segment. The letter will fuse on the midline with its opposite counterpart to become the basilar artery[1]. A mesencephalic artery supplying the tectal region and arising from what can be considered the P1 segment, becomes the posterior cerebral artery, by distal annexation of the distal cortical supply (occipital and medial parietal) of the anterior choroidal artery[1,2].The basilar artery will be formed after fusion of the longitudinal neural artery, in front of the pontomesencephalic sulcus in relation to regression of the trigeminal arteries. These arteries determine the site of flow reversal in the distal basilar system, and the level of division(or fusion) of the basilar artery[3]. The later the trigeminal artery involution occurs, the lower the role of the vertebral flow in the supply to the mesencephalic region. In such a situation, the carotid contribution remains dominant, and a caudal fusion disposition is likely. Finally, three types of basilar tip anatomical disposition have been described[3]. Each of them corresponds to the fusion of both caudal internal carotid divisions on the midline: symmetrical cranial, symmetrical caudal, and asymmetrical. The angiographic landmark to differentiate the basilar-tip disposition consists mainly of the site of origin of the SCA. The SCA arising from P1 corresponds to the caudal fusion disposition. When the SCA arises from the basilar trunk, it corresponds to a cranial one. Such arrangement can be bilateral or symmetrical; in other instances the origin of the SCA is different on each side and subsequently described as asymmetrical (caudal on one side, cranial on the other one). In cases of P1 absence, the anatomical disposition is similar to the asymmetrical fusion[3].

The terminal bifurcation of the basilar artery with in the interpeduncular cistern bifurcates 1-3 mm distal to the origin of the superior cerebellar artery inferior to the much larger paired posterior cerebral arterie. From its origin the posterior cerebral artery curves superior to the oculomotor nerve in relation to theantero medial portion of the peduncle and joins the posterior communicating artery. This segment of the posterior cerebral artery from its origin to the posterior communicating artery is termed the P1 segment[4]. The thalamoperforating arteries consist of one ormore arteries usually originating on the central segment of P1; but occasionally originating from the medial 1

mm P1(8%) or the lateral 1 mm (5%)[5] or rarely even arising from the posterior portion of the posterior communicating artery. Saeki and Rhoton (1977) found that the P; branch nearest the bifurcation was the largest branch of P, in 56 per cent of cases and almost always was a thalamoperforating artery[6]. Lang and Brunner (1978) described four patterns of thalamoperforating arteries in an examination of 50 cadaver brains. In type I (20%) bilateral, multiple thalamoperforating branches were seen from P1, In type II (26%) only one side had multiple thalamoperforating branches, as the other P1 had 1-2 larger "stem" thalamoperforating arteries arising that then divided into 3-8 branches. In type III (42%), both P1 segments had larger stem thalamoperforating branches, and finally type IV (8%), one P1 had no thalamoperforating branches, while the other had a large stem thalamoperforator that supplied branches bilaterally[5].

Knowledge of the microvascular features of the thalamoperforating arteries is of paramount importance for surgeons approaching vascular lesions of this area, particularly basilar top aneurysms, and also importance for neurologist and neurointerventionist for ischemic lesion involving basilar artery(BA) and P1 segment of posterior cerebral arteries (PCA).

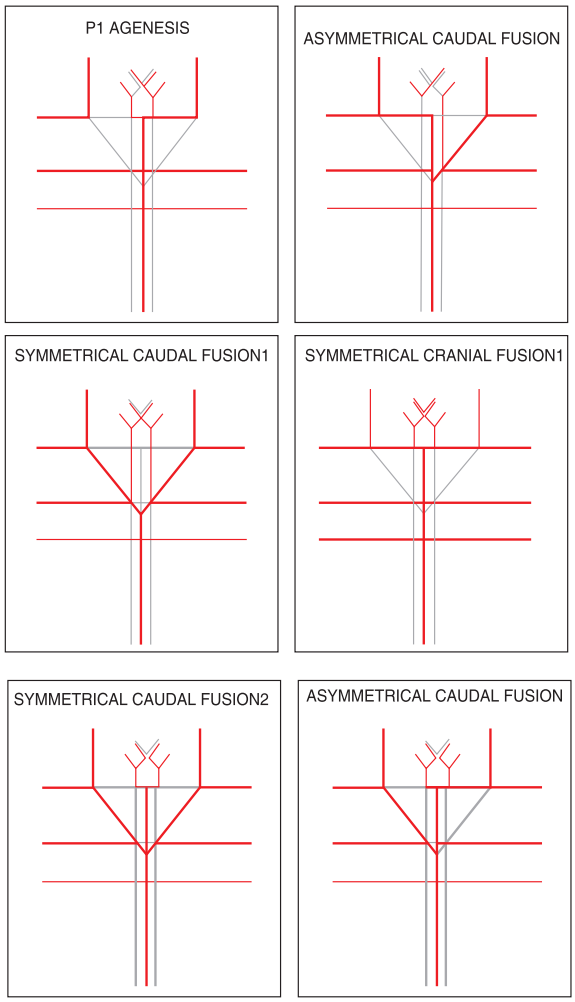

Figure A: Distal basilar variations. The general pattern and several fusion type. © P. Lasjaunias

Materials and Methods

This observational study was conducted in the department of Neurointervention of Max Super-specialty Hospital, New Delhi, India and Neo multispecialty Hospital, Noida, UP, India during July 2016 to December 2016. All collected data were checked, edited and analyzed by using computer based SPSS software version 16.0. Data were presented by frequency distribution and percentage.

A total of 76 patients admitted in the Neurointervention department for digital subtraction angiography (DSA) included in this study. Sampling technique was purposive. The angiogram machine was SIEMENS Artis Zee 3040 system and framing rate was 4frame/sec. Analysis of distal basilar tip anatomy, origin and distribution of perforating arteries from P1 segment was done. The angiographic landmark to differentiate the basilar-tip disposition consists mainly of the site of origin of the SCA. The SCA arising from P1 corresponds to the caudal fusion disposition. When the SCA arises from the basilar trunk, it corresponds to a cranial one. Such arrangement can be bilateral or symmetrical, in other instances the origin of the SCA is different on each side and subsequently described as asymmetrical (caudal on one side, cranial on the other one). In cases of P1 absence, the anatomical disposition is similar to the asymmetrical fusion.

Origin of thalamoperforating arteries were studied and classified into five different types according to their origin at the P1 segment and drawn in data collection sheet :Type I (Bilateral multiple), multiple branches arose from the P1 segment on each side ; Type II (Unilateral single, unilateral multiple), a single branch on one side of P1 segment and multiple branches on the other side ; Type III (Bilateral single), asingle thick branch on each P1 segment; Type IV (Unilateral single), unilateral single and other with no branch; Type V (Unilateral multiple) : unilateral multiple and the other with no branch.

Results

Out of the 76 patients, 43(56.5%) were belonged to 50 and over 50 years And under 50 years were 33 (43.4%) Table .

Table I: Distribution of the cases by age (n=76)

Age (in year)	Number of patients	Percentage
≥50	43	56.5
<50	33	43.4

It was observed 51 (67.1%) were male and 25 (32.8%) were female. Male to female ratio was 2.04:1 (Table II).

Table II: Distribution of the cases by sex (n=76)

Sex	Number of patients	Percentage
Male	51	67.1
Female	25	32.8

Analysis of basilar tip anatomy among the cases, 60 (78.9%) were caudal fusion, where as 16 (21.0%) were cranial fusion. Table-III

Table III : Distribution of Basilar tip disposition among cases (n=76)

Fusion type	Number of cases	Percentage
Caudal	60	78.9
Cranial	16	21.0

Among the caudal fusion group 35 (46.0%) was seen asymmetrical and 25 (32.8%) was symmetrical disposition. Cranial symmetrical fusion was found in 16 (21.0%) cases(Table-IV).

Table IV: Distribution of Basilar tip disposition among cases (n=76)

Fusion type	Number of cases	Percentage
Caudal symmetrical	35	46.0
Caudal Asymmetrical	25	32.8
Cranial symmetrical	35	21.0

Analysis of morphological variation of P1 segment showed that 5.2% were hypoplastic in left P1 segment and P1 agenesis were observed 3.9% (1.3% in right and 2.6% in left) Table-V.

Table V: Characteristics of P1 segment among cases (n=76)

Characteristics of P1	Number of cases	Percentage
Right P1hypoplastic	0	0.0
Left P1hypopalstic	4	5.2
Right P1 agenesis	1	1.3
Left P1 agenesis	1	2.6

Origin of P1 thalamoperforating branches were studied and classified into five different types whether they arise from left or right P1 segment or from both sides either single trunk or multiple branches: Type I was observed in 38.1% cases, Type II in 27.6% cases, Type III in 17.1% cases,Type IV in 7.8% cases and Tpe V was found in 9.2 cases.(Table-VI).

Table VI: Distribution of origin ofthalamoperforators of p1 segment (n=88)

Origin of perforators	Number of cases	Percentage
Type I	29	38.1
Type II	21	27.6
Type III	13	17.1
Type IV	6	7.8
Type V	7	9.2

Discussion

The Distal basilar anatomy and the perforating branch of distal basilar artery were studied by many authors in cadaveric brain in detail[3,7-12,13,14] but very few data exists regarding angiographic studies of basilar tip anatomy and its relation with perforating branches of P1 segment of posterior cerebral artery using digital subtraction angiography[3].

In order to understand the origin and course of the arteries in the interpeduncular fossa, two embryo logic facts must be taken into account[3]. The internal carotid artery divides into two terminal branches: a cranial branch and a caudal . The caudal branch composed of the future posterior communicating artery, which is connected to the future P1segment of the posterior cerebral artery. This last artery reaches the ipsilateral ventral longitudinal neural artery. The superior segment of the basilar artery is the result of both neural arteries merging at the level of the primitive trigeminal arteries first, and then on cranially. For either side, the timing of this merging depends on the date at which the corresponding trigeminal artery regresses. Thus the dates of regression of the trigeminal arteries, whether identical or not, determine the moment at which the blood flow reverses in the basilar artery, but also the configuration of the upper basilar artery and of both P1 segments (superior basilar complex). Initially, the posterior cerebral artery is a mesencephalic artery[15], and later a mesencephalo-diencephalic artery. It finally becomes a mesencephalo-diencephalic and telencephalic artery by annexing the distal territory of the anterior choroidal artery.[14]

In our study angiographic analysis of basilar tip anatomy among the cases showed 78.9% were caudal fusion, where as 21.0% was cranial fusion. Among the caudal fusion group 46.0% was Asymmetrical and 32.8% was symmetrical disposition. Cranial symmetrical fusion was found in 21.0 % cases.Analysis of morphological variation of P1 segment showed that 5.2% were hypoplastic in left P1 segment and P1 agenesis were observed 3.9% (1.3% in right and 2.6% in left)

According to Lasjaunius[3] analysis of the basilar tip anatomy in a case control study, control angiographic group of 46 cases without basilar tip aneurysm showed 30.4 % of cranial symmetrical fusion, whereas the 69.6% remaining had the caudal fusion disposition (26,1 % symmetrical, 43,5% asymmetrical, 2,8% with unilateral absence of PI). Our observation was correlated well with this findings. The conclusion of Lasjaunius concerning the SCA, an embryologic branch of the internal carotid artery, its origin are always associated with a late and low merging of the P1 segment.

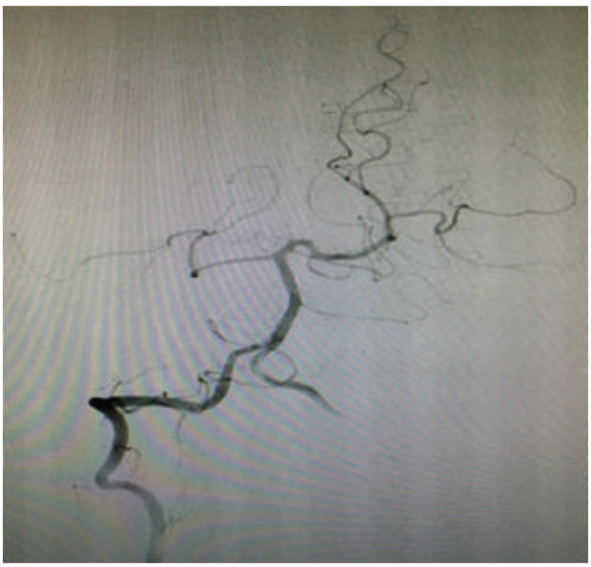

Figure A: Asymmetrical caudal fusion of basilar artery with P1 agenesis(right)

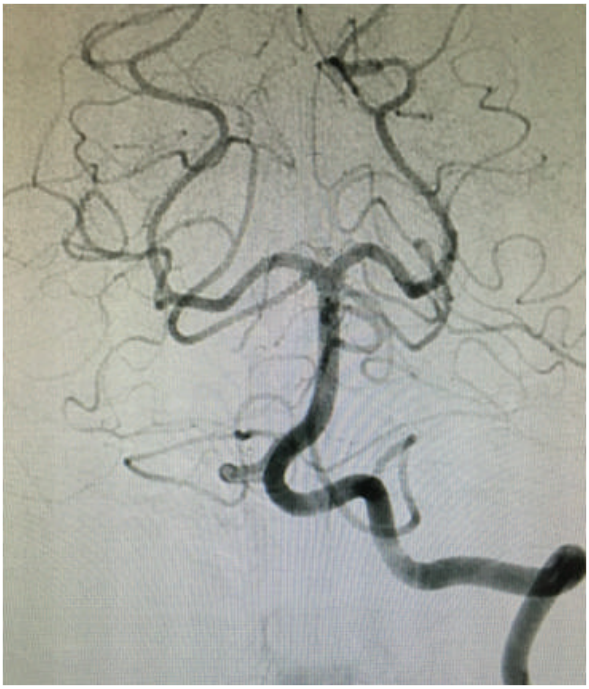

Figure B: Asymmetrical caudal fusion of basilar

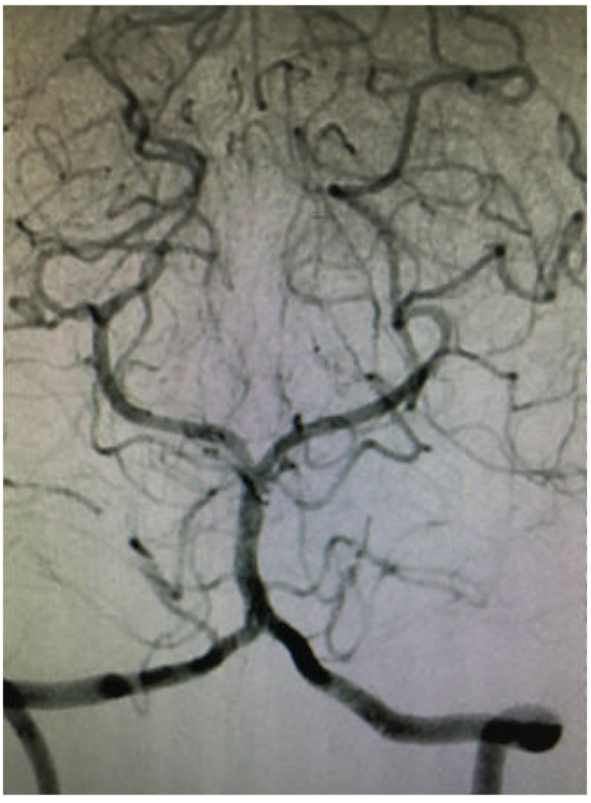

Figure C: Symmetrical caudal fusion

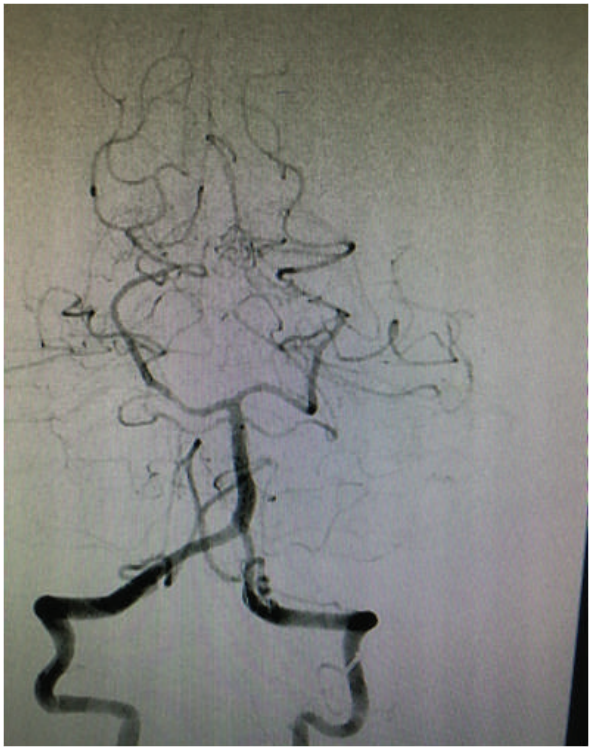

Figure D: symmetrical cranial fusion

Origin of P1 thalamoperforating branches were studied and classified into five different types whether they arose from left or right P1 segment or from both sides either single trunk or multiple branches: Type I was observed in 38.1% cases, Type II in 27.6% cases, Type III in 17.1% cases,Type IV in 7.8% cases and Type V was found in 9.2 cases.

SukhQue Park, M.D.et al[16] described thalamoperforating arteries into five different types according to their origin at the P1 segment :Type I (Bilateral multiple), multiple branches arose from the P1 segment on each side (10 cases, 38.5%), Type II (Unilateral single, unilateral multiple), a single branch on one side of P1 segment and multiple branches on the other side (7 cases, 26.9%), Type III (Bilateral single), a single thick branch on each P1 segment (5 cases, 19.2%),Type IV (Unilateral single), unilateral single branch and the other with no branch (3 cases, 11.5%), Type V (Unilateral multiple) : unilateral multiple and the other with no branch (1 case, 3.8%).

In bilateral 52 P1 segments of 26 specimens, multiple thalamoperforating arteries more than two arising from the P1 segment were noted in 28 P1 segments (53.8%) and single thalamoperforating artery was noted in 20 P1 segments (38.5%). In 3 specimen (11.5%), P1 segment had a single thick branch on one side and had no branch on the other side. If this branch arises as a single thick artery, damage to this artery during surgery may cause serious neurological insufficiency.

In our study the most frequent disposition was either a double truncus on one side or a single truncus on the other hand, and multiple trunks were well correlated with this observation.

Gunnal SA et al[17]. described morphological variations of P1 in a

cadaveric study, which included aplasia, hypoplasia, duplication, fenestration, and an unusual origin. The morphological variations of P1 were seen in 22 specimens (12.94%). Aplasia was seen in 4 specimens (2.35%), hypoplasia in 9(5.29%), duplication in 4 (2.35%), fenestration in 2 (1.17%), and common stem of origin with SCA in 3 (1.76%). In our study analysis of morphological variation of P1 segment showed that 5.2% were hypoplastic in left P1 segment and P1 agenesis were observed 3.9% (1.3% in right and 2.6% in left).

Pedroza[11] described five possible models to explain the origin and number of arteries (from nine to five), based on the configuration of the opposite side: single truncus on one side, single truncus on either side, double truncus on one side, single truncus one side and double truncus on the other side and multiple truncus. He also reported that about 10% of P1 segments the perforators originated from only one trunk, so occlusion would always cause bilateral thalamopeduncular infarct.

SukhQue Park[16] observed five (19.2%) of cases, perforators arose from the P1 segment on each side as a single thick branch. There was only a single thick branch on one side in 11.5% of cases. In such cases the opposite side was supplied by this branch. If this branch arises as a single thick artery, damage to this artery during surgery may cause serious neurological insufficiency. The number and diameter of perforating branches were relatively constant, regardless of the P1 segment size;

therefore, a hypoplastic posterior communicating artery or P1 segment supplied the same perforating area as a larger vessel despite its smaller size. This fits with our finding, so the importance of preservation of these vessels deserves emphasis because of the important role of a hypoplastic vessel in supply of the local area.

Zeal[18] observed 25 injected brains, and found two P1 segments with no perforating branch (one was normal and other was fetal). He also found that the perforating branches always originated from the posterior to superior walls of P1, which was not evaluated in our study.

Limitations

Variations between the cases in our study may be due to lack of detectability of the small vessels, Incomplete or delayed filling of the contrast material in the smaller and terminal branches or incomplete anatomic feature[19-22].

Conclusion

Potential future developments should focus on a continuous improvement of image quality and further refinement of technological advances or concepts to increase reliability of distal basilar perforating vessels angiography. Dedicated angiographic protocols with optimization of scan time, iodine concentration, and injection parameters of contrast materials may provide future options to use this data for risk assessment of patients with arterial occlusive or stenotic disease or aneurysms before endovascular treatment with angioplasty and stent placement.

References:

01. Padget DH: The cranial venous system in man in reference to development adult configuration, and relation to the arteries. Am J Anat 98: 307-356, 1956.

02. Moffat DB: The development of the posterior cerebral artery. J Anat 95: 485-496, 1961.

03. Lasjaunias P, Berenstein A: Surgical neuroangiography. Vo!. 3: Functional anatomy of brain, spinal cord and spine. Springer Verlag, Berlin 1990.

04. Krayenbuhl, H., M. G. Ya§argil: Cerebral Angiography, 2nd Ed.Lippincott, Philadelphia 1968

05. Lang J, Brunner FX :Über die rami centrales der aa. Cerebri anteriorand media.Gegenbaurs Morph Jb124 : 364, 1978

06. Saeki N, Rothon AL: Microsurgical anatomy of the upper basilar artery and the posterior circle of Willis. J Neurosug 46: 563-577,1977.

07. Hardy DG, Peace MS, Rhoton AL: Microsurgicalanatomy of the superior cerebellar artery. Neurosurgery 6: 10-28,1980.

08. Lazorthes G, Gouaze A, Salamon G: Vascularisationetcirculation de l'encephale. Tomes I et 11. Masson, Paris 1976.

09. Marinkovic S, Gibo H: The surgical anatomy of the perforating branches of the basilar artery. Neurosurgery 33: 80-87, 1993.

10. Marinkovic S, Milisavljevic M, Kovacevic M: Interpeduncular perforating branches of the posterior cerebral artery. Microsurgery of their extracerebral and intracerebral segments.SurgNeurol 26: 349-359, 1986.

11. Pedroza A, DujovnyM et Al: Microvascularanatomy of the interpeduncular fossa. J Neurosurg 64: 484-493,1986.

12. Percheron G: Les arteres du thalamus humain, 11: arteresetterritoires-thalamiquesparamedians de l'arterebasilairecommunicante. Rev Neurol 132: 309-324,1976.

13. Christoph J:An anatomic study with potential neurosurgical and neuroendovascularimportence .British Journal of neurosurgery vol 28 issue 1, 2014

14. Brassier G, Morandi X et al.: Origin of the perforating arteries of the interpeduncular fossa in relation to the termination of the basilar artery. Interventional Neuroradiology4:109-120,1998.

15. Kaplan Ha, Ford Hd: The brain vascular system. American Elsevier, Amsterdam 1996.

16. SukhQue Park, M.D, Hack-Gun Bae, M.D: Morphological Characteristics of the Thalamoperforating Arteries. J Korean NeurosurgSoc47 :36-41, 2010

17. Gunnal SA, Farooqui MS Wabale RN,:Hindawi Publishing Corporation Anatomy Research International Volume 2015, Article ID 681903, 10 pages

18. Zeal AA, Rhoton AL: Microsurgical anatomy of the posterior cerebral artery. J Neurosurg 48: 534-559, 1978.

19. Duvernoy HM. Human Brain Stem Vessels.Berlin Heidelberg: Springer-Verlag; 2010

20. Pai BS, VarmaRG, Kulkarni RN, et al. Microsurgical anatomy of the posterior circulation. Neurol India 2007;55:31–41

21. Pais D, Arantes M, Casal D, et al. Brain stem arteries in Canisfamiliaris–implications in experimental procedures. Braz J MorpholSci2009;26:8–11

22. PercheronG : The anatomy of the arterial supply of the humanthalamus and its use for the interpretation of the thalamic vascularpathology. Z Neurol205: 1-13, 1973

Review Article

A Review of PCSK9 Inhibitors

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ABSTRACT

Elevated LDL cholesterol is one of the most important factor of atherosclerotic vascular disease, a primary cause of premature cardiovascular mortality and morbidity.Many randomised, controlled trials have proven the utility of statins in reducing LDL cholesterol and cardiovascular disease during the last 25 years. But we need to go beyond the limitations of statins. The next generation of treatments to control elevated LDL cholesterol must address the substantial residual cardiovascular risk remaining after even intensive statin-based therapy.An exciting new treatment for marked reduction of LDL cholesterol levels is now on the horizon: the PCSK9 inhibitors.

Key words: *PCSK9 (Proprotein convertase subtilisin/kexin type 9)*

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Introduction

About one death in four occurred as a result of diseases of the heart, with the majority due to coronary heart disease (CHD.[1,2] Elevated LDL cholesterol accelerates atherosclerosis and increases the likelihood of death or disability due to cardiovascular disease.[3,4] LDL cholesterol remains the key target of lipid-modifying therapy. Lipid-modifying therapy provide marked reductions in LDL cholesterol and clinically significant reductions in cardiovascular event rates in patients at high cardiovascular risk.[5,6] Nevertheless, most patients do not achieve their goal LDL cholesterol on these agents, particularly people with the severe hypercholesterolaemia associated with familial hypercholesterolaemia. Many patients with elevated LDL cholesterol not due to familial hypercholesterolaemia do not achieve LDL cholesterol goals with current treatments due to variable LDL cholesterol responses and nonadherence to statins.[7]

There remains a need for a consistently effective, well-tolerated treatment that will provide reductions in LDL cholesterol beyond those available with a statin, with reductions in other atherogenic lipoproteins, including VLDL cholesterol, lipoprotein remnants and lipoprotein that will address the residual risk after treatment with a statin.Current therapies are targeted at reducing the rate of cholesterol biosynthesis (the main effect of statins) or reducing the rate of absorption of cholesterol into the circulation (ezetimibe, bile acid sequestrants or plant sterols/stanols) derived from food and/or from bile. The majority of circulating LDL cholesterol is synthesised in the liver, by HMG-CoA reductase and the principal means of removal of LDL cholesterol from the circulation is via a family of hepatic LDL receptors. The LDL receptor on the surface of liver cells is an essential component of the machinery for regulating levels of LDL cholesterol. LDL particle binds to this receptor, taken up within an intracellular endosome, and then catabolised within a lysosome. The lipid and protein content of the LDL particle is then degraded.[8] Most (90–95%) patients with familial hypercholesterolaemia have mutations in the LDL Rgene that result in reduced or abolished LDL receptor function or a reduced number of LDL receptor protein molecules on the cell surface.[9]

What is PCSK9 and how does it influence circulating levels of LDL-C:

The hepatic LDL receptor is the most important mechanism of removal of LDL cholesterol from the circulation. The binding of the PCSK9 protein to the LDL receptor increases the probability of the LDL receptor being degraded by lysosome, rather than being recycled to the cell membrane.[10,11] A number of mutations and polymorphisms of the PCSK9 gene have been identified, which support its importance in the regulation of LDL cholesterol. These include “loss of function” and “gain of function” mutations that respectively reduce and increase the activity of PCSK9. People with mutations of the PCSK9 gene that decrease its activity have lifelong low LDL cholesterol and a lower risk of cardiovascular events than the general population. On the other hand, mutations of the PCSK9 gene that increase its activity can give rise to the familial hypercholesterolaemia phenotype.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition is a novel therapeutic concept based on reduction of plasma LDL cholesterol through increased hepatic clearance. It acts by reducing the activity or expression of PCSK9 that increases the number of LDL receptors which reduces circulating LDL cholesterol.[12] PCSK9 inhibitors reduced LDL cholesterol by >50% in randomised trials in patients with hypercholesterolaemia, Substantial reductions in LDL cholesterol were also seen in patients with familial hypercholesterolaemia, PCSK9 inhibitors are effective when added to other lipid-modifying treatment, including high-intensity statin therapy,reduced frequency of adverse cardiovascular outcomes associated with a PCSK9 inhibitor in patients with hypercholesterolaemia.[13]

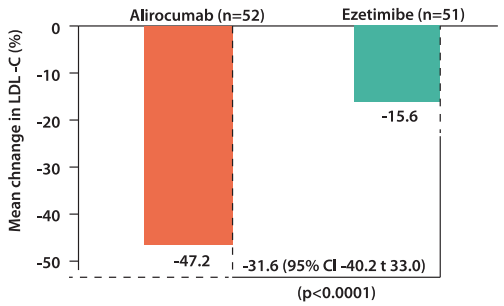
A number of PCSK9 inhibitors are currently in clinical develop-

ment.Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the US Food and Drug Administration (FDA) has recommended approval of evolocumab and alirocumab for therapeutic use.[14,15,16,17] These are monoclonal antibodies which must be given bysubcutaneous injection. They have a long duration of action requiring infrequent administration compared with current therapies

• Evolocumab (Amgen) This agent has been evaluated using 2-weekly (140 mg dose) or monthly (420 mg dose).

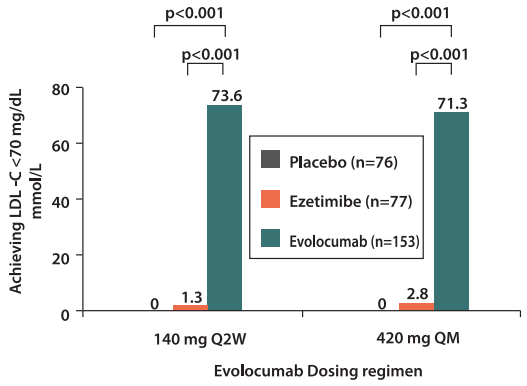
• Alirocumab (Sanofi/Regeneron)administration of 75–150 mg of this agent at 2-weekly intervals

Figure 4.2. Effects of 24 weeks of treatment with ezetimibe on LDL cholesterol in patients with



Drawn from data presented by Raal. Doses given were 75 mg s.c. Q2w for alirocumab and 10 mg QD for ezetimibe. Patients were not receiving other lipid lowering treatment.

Figure 4.3. Proportions of patients achieving LDL-C <0 (1.8 mmol/L) in the MENDEL-2



Q2W: dosing every two weeks; QM: monthly dosing. Number of patients: n=153 for each evolocumab group. Drawn from data presented by Robinsen

Side effects

PCSK9 inhibitors have been generally well tolerated in clinical trials. The main side-effects associated with these agents are injection site reactions, which is not uncommon for an injectable treatment. The tolerability and safety profiles of these agents so far support long-term administration for lifelong conditions such as hypercholesterolaemia.[18, 19, 20] People at high cardiovascular risk who are likely to benefit from treatment with a PCSK9 inhibitor

• People with familial hypercholesterolaemia

• People with statin intolerance

• People at high cardiovascular risk who are not at their LDL cholesterol goal.

References:

1. Centers for Disease Control and Prevention. Heart Disease facts and statistics (2013). Deaths: Final data for 2013. National Vital Statistics Report. 2015;64(2) Available at http://www.cdc.gov/heartdisease/statistics.htm (accessed February 2015).
2. Navar-Boggan AM, Peterson ED, D'Agostino RB et al. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. Circulation2015;131:451-8.
3. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33:1635-701.
4. Stone NJ, Robinson JG, Lichtenstein AH et al. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. Ann Intern Med2014;160:339-43.
5. Ference BA, Yoo W, Alesh I et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol2012;60:2631-9.
6. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. CurrAtheroscler Rep 2012;14:1-10.
7. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care 2008;31:811-22.
8. Go GW, Mani A. Low-density lipoprotein receptor (LDLR) family orchestrates cholesterol homeostasis. Yale J Biol Med 2012;85:19-28.
9. Peterson AS, Fong LG, Young SG. PCSK9 function and physiology. J Lipid Res 2008; 49: 1152-6.
10. Poirier S, Mayer G. The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. Drug Des DevelTher 2013; 7:1135-48.
11. Cameron J, Holla ØL, Ranheim T, Kulseth MA, Berge KE, Leren TP. Effect of mutations in the PCSK9 gene on the cell surface LDL receptors. Hum Mol Genet 2006;15:1551-8.
12. Abifadel M, Guerin M, Benjannet S et al. Identification and characterization of new gain-offunction mutations in the PCSK9 gene responsible for autosomal dominant hypercho-

lesterolemia. Atherosclerosis 2012;223:394-400

13. Blom DJ, Hala T, Bolognese M et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med2014; 370:1809-19.

14. Roth EM, Taskinen MR, Ginsberg HN et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol 2014;176:55-61.

15. Raal FJ, Honarpour N, Blom DJ et al.Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2014;385(9965):341-50.

16. Raal FJ, Stein EA, Dufour R et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet2014;385(9965):331-40.

17. Robinson JG, Nedergaard BS, Rogers WJ etal.Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA2014;311:1870-82

18. Stein EA, Giugliano RP, Koren MJ. Efficacy and safety of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, in hyperlipidaemic patients on various background lipid therapies: pooled analysis of 1359 patients in four phase 2 trials.Eur Heart J2014;35:2249-59.

19. Sabatine MS, Giugliano RP, Wiviott SD et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1500-9.

20. Robinson JG, Farnier M, Krempf M et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489-99.

Review Article

Ulipristal Acetate for uterine fibroid

Nasreen S[1], Tasmin KS[2], Ahmed S[3]

ABSTRACT:

Fibroids are the most common tumors of women during their reproductive life and they are found in one out of every four women. They are symptomatic in 50% of the women who have them, with the peak incidence of symptoms occurring among women in their 30s and 40s. Fibroids can cause a variety of symptoms which include menstrual disturbances (commonly menorrhagia and dysmenorrhea), pressure symptoms such as increased urinary frequency, pelvic pain and constipation, they may also interfere with reproduction. Although it is usually assumed that problems associated with fibroids resolve with the onset of the menopause, in reality fibroids can cause symptoms (including abnormal bleeding) even in the menopause. UlipristalAcetate (UPA) is an oral selective progesterone receptor modulator. As progesterone promotes the growth of uterine fibroids, blocking its receptor may reduce their size. The dose used for this indication can inhibit ovulation and lead to amenorrhoea which will be of benefit to women who have heavy menstrual bleeding related to their fibroids.

Keywords: *Uterine fibroid, ullipristal acetate.*

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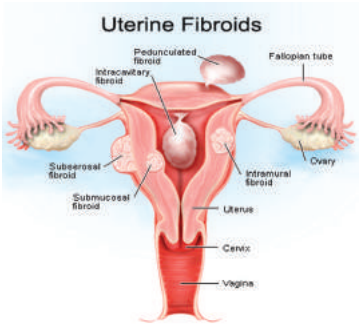
Introduction

Majority of symptomatic uterine fibroids are currently treated by surgical interventions (myomectomy or hysterectomy) or radiological treatments (uterine artery embolization or focused ultrasound surgery). None of these treatments are a panacea for every woman, and what is conspicuous is the lack of an effective long-term medical therapy for a disorder so common among women of reproductive age. Treatment should begin in the first week of a menstrual period. The single daily dose is rapidly absorbed. There is extensive metabolism involving cytochrome P450 3A4. Ulipristal should therefore not be taken with inducers of this enzyme, such as carbamazepine, phenytoin and St John's wort, or with inhibitors such as erythromycin. The half-life of ulipristal is about 38 hours with most of the metabolites being excreted in the faeces. No studies have been done in women with impaired hepatic or renal function.



Discussion

Ulipristal acetate is a progesterone receptor modulator that has previously been approved as a postcoital contraceptive.[1]

The approval of ulipristal for the treatment of fibroids appears to have been mainly based on four trials (see Table).2-5 PEARL I and II were short term while PEARL III and IV studied repeated courses of treatment.

Table
Efficacy of Ulipristal in women with fibroids

Trial	Total number of Patients	Duration of treatment	Progress
Pearl II	242	13 weeks	73%
Pearl III	337	13 weeks	75%
Pearl IV	209	12-weeks courses	-

Table: Efficacy of ulipristal in women with fibroids

Single three-month course

PEARL I enrolled women with anaemia as a result of heavy periods related to fibroids. These women were planning to have surgical treatment. There was a placebo group of 48 women, while 96 were randomised to take ulipristal 5 mg and 98 to take ulipristal 10 mg. After 13 weeks, bleeding was significantly reduced in more than 90% of the women taking ulipristal compared with 19% of the placebo group. Amenorrhoea was reported by 73% of the women taking ulipristal 5 mg and by 82% of those taking 10 mg. Only 6% of the placebo group had amenorrhoea. MRI showed that the median total fibroid volume had decreased by 21% with ulipristal 5 mg and by 12% with 10 mg while there had been a 3% increase in the volume measured in the placebo group.[2]

PEARL II enrolled 307 women with heavy bleeding who were eligible for surgical treatment of their fibroids. In this trial daily ulipristal was compared to monthly injections of leuprorelin, an agonist of gonadotrophin-releasing hormone. After 13 weeks,

bleeding had been controlled in 90% of the women who took ulipristal 5 mg and 98% of those taking 10 mg. It was also controlled in 89% of the women given leuprorelin. These differences showed ulipristal was not inferior to leuprorelin, but leuprorelin had a greater effect on fibroid size. The total volume of the three largest fibroids in each patient was reduced by a median of 36% with ulipristal 5 mg, 42% with ulipristal 10 mg and by 53% with leuprorelin.[3]

Repeated courses

In PEARL III 209 women with heavy bleeding and at least one fibroid took open-label ulipristal 10 mg for three months. This was followed by double-blind treatment with norethisterone or a placebo for 10 days. The women could then opt to repeat this regimen up to three times giving a total of up to four courses. The primary outcome of the study was amenorrhoea. This was achieved by 79% of the women after the first course of ulipristal. Among the 107 women who had four courses of treatment, 90% had amenorrhoea. The three largest fibroids, seen on ultrasound scans, shrunk by a median of 45% after one course and 72% after four courses. In the women who took norethisterone, menstruation resumed more rapidly and blood loss was less than in the placebo group.[4]

PEARL IV had a similar study population and also had amenorrhoea as a primary end point. The 451 women were randomised to take ulipristal 5 mg or 10 mg in 12-week courses. The interval between each course depended on the timing of menstruation. At the end of each of the first two treatment courses 62% of the women taking 5 mg and 73% of those taking 10 mg had amenorrhoea[5]. For patients who completed the protocol of four treatment courses the corresponding figures were 63% and 73%. After four treatment courses the three largest fibroids seen on ultrasound had reduced in volume by around 72% in both groups.[6]

The common adverse effects of ulipristal include headache, nausea and abdominal pain. The actions of ulipristal may cause some women to experience hot flushes. The effect of repeated courses on fertility is uncertain. For most women menstruation resumes within a month of stopping ulipristal.[4,5]

Conclusion

The role of ulipristal will be determined by each patient's problems. While surgery will remove fibroids, this may not be appropriate for women planning a future pregnancy. It is possible that ulipristal could reduce the size of the fibroids to enable less invasive surgery. For women who do not want surgery more research will be needed on repeated courses of ulipristal.

REFERENCES

1. Ulipristal acetate. Aust Prescr 2016;39:228-9. 10.18773/austprescr.2016.082 [Cross Ref]
2. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. PEARL I Study Group .Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409-20. 10.1056/NEJMoa1103182 [PubMed] [Cross Ref]
3. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al. PEARL II Study Group . Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421-32. 10.1056/NEJMoa1103180 [PubMed] [Cross Ref]
4. Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, et al. PEARL III and PEARL III Extension Study Group . Long-term treatment of uterine fibroids with ulipristal acetate. FertilSteril 2014;101:1565-73.e1. 10.1016/j.fertnstert.2014.02.008 [PubMed] [Cross Ref]
5. Donnez J, Hudecek R, Donnez O, Matule D, Arhendt HJ, Zatik J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. FertilSteril 2015;103:519-27.e3. 10.1016/j.fertnstert.2014.10.038 [PubMed] [Cross Ref]
6. Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J, et al. Long-term medical management of uterine fibroids with ulipristal acetate. FertilSteril 2016;105:165-173.e4. 10.1016/j.fertnstert.2015.09.032 [PubMed] [Cross Ref]

Case Report

Wegener's Granulomatosis: A Case Report

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ABSTRACT

Wegener's granulomatosis is an autoimmune condition, characterized by granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels (e.g. capillaries, venules, arterioles & arteries) with necrotizing glomerulonephritis. The pathological hallmark is the co-existence of vasculitis and granulomas and classically involves a triad of airway, lung and renal disease. Our patient was Mrs. Nasima, 54 years old lady who was admitted with the complaints of mild headache with occasional blood stained nasal discharge, nasal obstruction for 8 years. She had long standing cough with productive sputum as well as progressive malaise. She developed hearing loss with tinnitus for last 5 months. She had saddle nose, malar prominence, and features of OME (otitis media with effusion). ESR of the patient was very high and chest CT scan reveals multiple cavitary lesion in both lung. Her C-ANCA was negative, but P-ANCA was positive. Audiometry reveals mixed type of hearing loss. Following exploration of nose and nasal cavity by lateral rhiniotomy approach some (reddish) tissue were taken and sent for histopathology which were consistent with Wegener's granulomatosis. After taking systemic corticosteroid and cytotoxic agent improvement of patient was noticeable and patient was discharged. Otolaryngologists need to be aware of this rare condition as it may mimic the symptoms of common ENT problems, like sinusitis, otitis media with effusion, allergy, etc. Earlier diagnosis , prompt necessary treatment and careful monitoring are needed to prevent irreversible, irrepairable consequences and complications.

Keywords: *Wegener's granulomatosis, auto immune, granulomatous condition, vasculitis.*

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Introduction

Wegener's granulomatosis is an autoimmune condition, characterized by granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels (e.g. capillaries, venules and arterioles) with necrotizing glomerulonephritis. The pathological hallmark is the co-existence of vasculitis and granulomas and classically involves a triad of airway, lung and renal disease. However, it is increasingly recognized that limited forms of the condition can occur.

The aetiology of Wegener's granulomatosis remains unknown. It's inflammatory nature represents some forms of hypersensitivity reaction with an immune response to an unknown stimulus. It may be related to inhaled bacteria which would explain the frequency with which the respiratory tract is involved. Though in small proportion of patient but deposition of immune complexes is thought to be responsible for vasculitis in other conditions. From an aetiological and diagnostic point of view, the most important finding of recent year is 2 main forms of ANCA could be found. Perinuclear or P-ANCA and Cytoplasmic or C- ANCA. In general, patients with Wegener's granulomatosis have C-ANCA, whereas P-ANCA (and occasionally also C-ANCA may be found in some other conditions, such as microscopic polyarteritis.

Case Report:

Our patient Mrs. Nasima, 54 years old muslim gentle lady was admitted into ENT Department, DMCH with the presenting complains of mild headache with history of occasional blood stained nasal discharge for 8 years. She developed long standing cough with foul smelling productive sputum for about 7 years. Patient developed progressive malaise with notably feeling of very unwell. At this occasion she came to our Department for short of hearing associated with tinnitus and mild earache for 5 months. On examination - ill looking, anxious patient had saddle nose, malar prominence with red eyes and a tiny suspicious reddish lesion in nasal cavity (on Diagnostic nasal endoscopy).on otoscopy her both tympanic membrane were dull, lusterless, and cone of light were absent. Patient also had features of bilateral cavitary lesions in lung. Her investigation reveals - Hb% - 10.2 gm/dl, ESR-135 mm in 1st hour, Chest X-ray P/A view-ill defined opacity was noted in Rt & Lt lungs, sputum for AFB - negative, Serum Creatinine - NAD. CT scan of PNS- maxillary, sphenoidal, ethmoidal sinusitis. DNS to rt with HIT (Lt), obstructed osteomeatal complex by thickened mucosa. CT scan of chest - bilateral multiple cavitary lesions with mediastinal lymphadenopathy. CT guided FNAC – could not be done, as lesion is covered by ribs. C-ANCA - negative, P-ANCA - positive.

Histopathology report - tissue and mucosa from Lt maxillary

antrum, lateral wall of nose, turbinates - Wegener's Granulomatosis.

PTA-Rt ear- moderate mixed type of hearing loss, Lt ear- moderately severe mixed type hearing loss, Impedance - Rt ear-'B' type curve, Lt ear- 'A' type curve, SRT- reduced (both ear).

Treatment: Tab Prednisolone, Deflazacort

Tab Methotrexate 5 mg, 1 tab weekly for 2 weeks, 2 tab weekly for 2 weeks, 3 tab weekly for 2 weeks, 4 tab weekly to be continued.

Tab Folic Acid

Patient was discharged from DMCH on 4th March, 2015. She felt much better during discharge. She had not aural, nasal, ocular, chest complains at all. She left the hospital walking on her feet quite normally with smiling face.

Discussion

Clinical features:

Any part of the body may be affected and in active cases this involvement may be widespread, at the onset. Previously, Wegener's granulomatosis remained a serious and lethal disease with patients frequently dying within a six to eight months period. The possibility of latent , incomplete and limited forms of the disease as well as the classic ' full blown' conditions is how recognized. Most patients start with relatively minor ENT symptoms, which may be overlooked by both the patient and the doctor.

Nasal symptoms:

The patient often complains of persistent cold or sinus. Associated epistaxis, nasal obstruction, excessive crusting, blood stained discharge, septal destruction and nasal collapse. There is no other condition which can give larger crusts than Wegener's granulomatosis. There is no gross destruction of the mid facial skin as seen in Stewart's granuloma / T-cell Lymphoma and basal cell carcinoma.

Pulmonary manifestations:

Involvement lung is manifested by cough, haemoptysis, pleuritic pain, single or multiple cavities in the lungs (on chest X-ray etc). Diagnosis may be aided by flexible bronchoscopy and lung biopsy (encapsulated lung abscess can be formed).

Renal manifestations:

Between 30 and 90 percent of patients will develop renal symptoms, although the organs may be spared in more limited forms of the disease. Both casts and red cells appear in the urine and early treatment is vital since damage is irreversible. S. Creatinine level is raised. Wegener's granulomatosis produces segmental or diffuse glomerulonephritis. Renal failure is the usual cause of death.

Ocular manifestations:

Conjunctivitis, dacryocystitis, episcleritis,corneal ulceration, optic neuritis, retinal artery occlusion, proptosis may occur in Wegener's granulomatosis. Blindness, unilateral or bilateral, is an important cause of morbidity in Wegener's Granulomatosis patients, inadequate and intermittent systemic therapy predispose this problem.

Oral manifestations:

Hyperplastic granular lesion of gingiva (beginning in the area of interdental papillae). If a tooth is lost , the socket may fail to heal. Extensive ulcerative stomatitis may occur.

Otological manifestations:

Patient may develop acute otitis media, otitis media with effusion. There may be deafness, pain and suppuration. Facial palsy has been recorded. Both conductive and sensorineural hearing loss may occur.

Laryngeal and tracheal manifestations:

Rare and affects the glottic and subglottic regions. threatening asphyxia, though insidious in its development. Tracheostomy may become necessary.

Other manifestations:

Skin ulceration, poly myalgia, polyarthritis may occur. Direct nervous system involvement is caused by granulomatous invasion of neural tissues, intracerebral or meningeal granulomas and neuritis vasculitis. Any cranial nerve may be involved. The ability of Wegener's granulomatosis to affect any organ in the body makes it a possible diagnosis in a wide range of obscure and bizarre clinical presentations.

Diagnosis:

Diagnosis of the condition relied in the past on clinical acumen supported by a high ESR, C-reactive protein and evidence of pulmonary and renal damage. The advent of the C-ANCA greatly assisted diagnosis, being highly specific and sensitive for the condition. However, a negative C-ANCA does not absolutely exclude the condition, particularly in the limited form and/ or when oral corticosteroids have been given. CT scan of the nose and PNS may show some midline destruction and often show opacification of the sinuses. This may be attributable to active granulomatous infiltration, burnt out disease with fibrotic change, or secondary infection. Unfortunately biopsy is not diagnostic, at best being described as consistent with Wegener's granulomatosis, but is helpful to exclude other pathology such as T-cell lymphoma.

ACR criteria:

Treatment:

Medical therapy includes systemic corticosteroids, a range of cytotoxic drugs (e.g. Cyclophosphamides and Azathioprime, Methotrexate), immunoglobulin infusions, cotrimoxazole and plasma exchange. Earlier diagnosis and careful monitoring have significantly improved the outcome for these patients, but the condition remains life threatening in its more severe forms. The nose is again managed with douching and topical corticosteroids. Surgery may be required for two infections but attempts to reconstruct the nose should be resisted until the disease has been quiescent for some years.

Conclusion:

Otolaryngologists need to be aware of this rare condition as it may mimic (common ENT disease) the symptoms of sinusitis, otitis media with effusion, allergy. Earlier diagnosis and necessary treatment and careful monitoring is needed to prevent irreversible, irreparable & dread complications, consequences.

References:

1. Howard DJ, Lund VJ, Granulomatous conditions of the nose,Gleeson M, Clarke R, Scott-Brown's Otolaryngology Head Neck Surgery, Edition 7th, Volume 2, Page 1649, Hodder Anold (Publishers) Ltd;2008
2. Lund VJ,Acute & Chronic Nasal Disorders, Ballenger JJ, Snow JB, Ballenger"s Otolaryngology Head & Neck Surgery, Edition 16th, Page-754-756, BC Decker Inc (Publishers);2003

Case Report

Polycystic Ovarian Syndrome & Hypothyroidism

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ABSTRACT:

Polycystic ovarian syndrome (PCOS) is the most common reproductive disorder, affecting up to 12 percent of all women. It is a disorder with many different faces, and it causes great emotional and physical distress to the millions of women worldwide who suffer from it. Women with PCOS are at risk for infertility and early pregnancy loss. Many are overweight, find it difficult to lose weight, and suffer with fatigue, depression and anxiety. There's a significant overlap of symptoms between PCOS and Thyroid Disease, Mrs.Shabana 24 years, housewife, came(08/08/15) to M fstc & 100 beded MCH hospital, Mohammadpur with the complains of married for 8 years but no issue. Her menstrual cycle was irregular. She was given some investigations of infertility (available in this hospital). Her Serum TSH : 18.00 µU/ml , USG of lower abdomen –PCOS . Other investigations and her husband`s semen analysis report were within normal range.She was given treatment of 1) Tablet Thyroxile (50mg) 1 tablet daily, 2) Tablet Metformin (500mg) 1 tablet twice daily, 3) Tablet (Folic Acid + Zinc) 1 tablet twice daily, all Rx given for three months. After few days(28/9/17) she took Tablet Thyroxine irregularly and gave history of two abortions .Then her Serum TSH and USG reports were as same as before.Then she was given : Tab Metformin (1+0+1), Tab Thyroxine (1+0+1), Cap E-cap (1+0+0), Folic Acid+ Zinc (1+0+1). On 31/01/17 she came with the history of Amenorrhoea for one and half months. Her urine PT was +ve , USG report showed : Single live pregnancy at 06 wks of gestational age.Her pregnancy period was uneventful . On 20/09/17 she was delivered a healthy male baby in this hospital.

Keywords: *Anovulation , Primary Subfertility, Hypothyroidism, Polycystic overy, Metformin.*

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Introduction

PCOS or PCOD (Polycystic Ovarian Syndrome and Polycystic Ovary Disorder, respectively) is a complex condition that can be difficult to diagnose. It's sometimes mistaken for a thyroid disorder, as some PCOS and thyroid symptoms are similar or they might occur together. In addition, the abnormalities in thyroid hormones can play a major role in PCOS, which is also often influenced by a condition called Insulin Resistance. It is possible that lifestyle changes, such as better diet, exercise, and pharmaceutical or nutritional supplementation, can correct many of the difficult symptoms you have with both disorders.

2 of the 3 following criteria are required for a diagnosis of PCOS (as defined by the Rotterdam Criteria):

1) Anovulation or Irregular Periods

2) Hyper-androgenism/elevated male hormone levels

OR Clinical hyper-androgenism: adult acne, hirsutism (a male pattern of body or facial hair), or hair loss (androgenic alopecia)

3) Polycystic appearing ovaries on ultrasound, containing multiple small follicles. Women with PCOS are at risk for infertility and early pregnancy loss. Many are overweight, find it difficult to lose weight, and suffer with fatigue, depression and anxiety. There's a significant overlap of symptoms between PCOS and Thyroid Disease, despite the fact that they are two very different conditions.

As part of a vicious cycle, the high testosterone in PCOS sparks even more insulin resistance[1]. You can get a general idea of how high levels of insulin contribute to the overall picture of PCOS as a result: the higher the insulin, the more severe hormonal dysregulations become.

Interestingly, research suggests that low thyroid function aggravates insulin resistance in PCOS[2]. On average, women with PCOS have higher TSH levels and are also more likely to have subclinical hypothyroidism when compared to age-matched controls without PCOS[3]. The National Academy of Clinical Biochemistry (NACB)'s laboratory guidelines state that >95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L[4]. Thyroid hormones increase the levels of SHBG[5]. A deficiency in thyroid hormones will make androgenic symptoms such as hair loss, acne, and hirsutism worse.

Case Report: Mrs. Shabana, 24 years old, house wife, wife of Mr. Motin (a shopkeeper) hailing from sher shah suri road , mohammadpur, Dhaka came on 08-08-2015 out patient department of infertility unit of Mfstc & 100 beded MCH hospital, mohammadpur, dhaka. Her complaints were trying for conception for 8 years but no issue. Her menstual cycle was irregular, her height 5′7″ weight 47 kg, average body build, her date of LMP was 2 months back.She was given some investigations-Urine-PT Blood grouping & Rh typing, Hb%, FBS, Blood sugar 2HAB, VDRL, HBsAg On D2/D3, S. FSH, LH, T3, T4, TSH, S. Prolactine.

Test for husband:

Semen Analysis, Blood grouping & Rh typing, VDRL, RBS,

HB_SAG, Her urine PT report was negative.

Then treatment given

Tab Nor ethisterone. 1+1+1- for 7 days.

On 21-08-15 her menstruation started. She came on 24-08-15. Then she was treated by Tab folic acid+zinc-for 3 months, Tab metformin (500 mg). 1+0+1 for 3 months.

On 22/08/15, Serum T3: 0.57 ng/ml, S.T4: 6.50 pmol/L, S.TSH: 18.00 µIU/ml, S prolactin: 9.00 ng/ml, S.FSH: 7.00 mIU/ml, S.LH: 4.50 mIU/ml, Usg of lower abdomen-bilateral PCOS

Then she was given Tab thyroxine (50 mg).1+0+1-to be continued

On her general examination: She was normotensive, blood group O positive,RBS-5.0 mg/dl. Her husbands semen analysis & other reports were normal. Then she was diagnosed as a case of primary sub-fertility due to bilateral PCOS & hypothyroidism. On 13-12-15. She came on the 2nd day of menstrual cycle. Then she was given tab latrazol (2.5 mg). 2+0+1 for 5 days. Tab Allylesterone (5 mg) from 16 th day of LMP for 10 days.

On 28-09-16 her TSH-17.50 µIU/ml because she discontinued tablet thyroxine. On 14-5-16 she gave history of abortion 2 times. On 4-12-16 she came to hospital. Then she was given treatment

Tab metformin 500 mg. (1+0+1).

Tab thyroxine 50 mg. (1+0+1).

Cap vit-E 400 mg. (1+0+0).

Tab folic acid+zinc. (1+0+1).

Cap microgest. (1+0+1).

Treatment for husband

Capsule vitamin E (but he discontinued)

On 31-01-17 she came with the history of amenorrhea for 1 & half months. Her urine for PT was positive USG 6 weeks alive pregnancy. She was given treatment of Tab folic acid+zinc. & Tab alleylestrona 5 mg. 1+0+1- for 4 months.

Then she was regular ANC checkup. Her pregnancy period was unevenful. Her S. TSH level was within normal range. On 20-09-17 she was delivered a healthy male baby in this hospital.

Figure 1: Polycystic Ovarian Syndrome

Discussion:

Polycystic Ovarian Syndrome (PCOS) is a hormonal imbalance that is implicated in a number of health issues. Because this condition is associated with the female reproductive system it might be baffling to learn that PCOS can also interfere with the thyroid. Since hormones have access to all areas of the body it makes sense that an imbalance in one set of hormones can lead to an imbalance in another. Because thyroid disorders are often caused by imbalances of the thyroid hormones, it naturally follows that Polycystic Ovarian Syndrome can actually cause you to be more susceptible to thyroid.

Figure 2: Thyroid gland

Disorders:

Polycystic Ovarian Syndrome (PCOS) can occur when the levels of androgens (male hormones) are too high in the body, although this is only one possible factor because some women with PCOS have normal testosterone levels. Mostly made up of testosterone, these androgens can wreak havoc on the female reproductive system, because they interfere with the natural levels of estrogen and progesterone. In doing so, they cause major changes in normal reproductive functions. These changes are reflected in the symptoms this condition can cause, many of which are painful, embarrassing, and difficult to express.

1. Infertility: Polycystic Ovarian Syndrome (PCOS) is one of the most common causes of female infertility, which is often the way women with this disease find out about their condition.
2. Polycystic Ovaries: Often compared to the image of a "string of pearls," polycystic ovaries are a common symptom of Polycystic Ovarian Syndrome (PCOS) but, despite the fact the condition is named after them, are not requisite for a positive diagnosis.
3. Hirsutism: Caused by excess levels of testosterone, this excessive growth of hair is a source of embarrassment and stress to many women. Oftentimes, hirsutism results in hair growth in unnatural and visible locations, such as the face, chest, or back.
4. Hair Loss: Often taking the form of male pattern baldness, hair loss or even thinning of the hair is an emotional and difficult symptom for women.

5. Weight Gain and Obesity: Difficult for women to cope with, especially considering modern pressures to maintain a thin figure, weight gain and obesity are common symptoms. In addition to gaining weight, many women have an extremely difficult time losing it.
6. Sporadic or Missing Menstrual Periods: This symptom can contribute to infertility and is caused by the interference of testosterone with the regular cycle of the female reproductive system.
7. Anovulation: Without ovulation, conception cannot be accomplished. This, then, is one of the major symptoms that leads to infertility and, like missing menstrual periods, is caused by the interference of testosterone. With high levels of testosterone, estrogen and progesterone cannot keep the female reproductive system on track.
8. Skin Conditions: Women with Polycystic Ovarian Syndrome (PCOS) often suffer through the embarrassment of having acne, skin tags, dry skin, dandruff, and other skin conditions. Included in this list of symptoms is acanthosis nigricans, which results in thick, dark patches of skin.
9. High Cholesterol and High Blood Pressure: These symptoms are extremely worrisome for women with Polycystic Ovarian Syndrome (PCOS) puting them at a greater risk for heart disease, heart attack, or stroke.
10. Sleep Apnea: This symptom makes every day harder, as women who cannot get a good night's rest are often exhausted.

Treatment for hypothyroidism often entails hormone replacement therapy, which helps get thyroid hormones to their proper levels. In fact, according to one endocrine research study, "In obese PCOS patients with primary hypothyroidism, Metformin (a diabetes drug) results in a signif cant fall and sometimes normalization of TSH, without causing any reciprocal changes in other thyroid function parameters."[6] Perhaps not ironically, Metformin is often prescribed to PCOS patients.

In both thyroid disorder though, a balanced diet and regular exercise are important to maintaining a high level of overall health, which will help your body fight these conditions and regain its proper hormonal levels.

Successfully managing Polycystic Ovarian Syndrome (PCOS) entails a complete system with five elements:

1. Eating a balanced diet.
2. Getting plenty of exercise.
3. Specially targeted formulas of vitamins, minerals, and botacals, these can help our body fight back.
4. Enlist emotional support.
5. Getting smart.

Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common endocrine disorders in the general population. Although the etiopathogenesis of hypothyroidism and PCOS is completely different, these two entities have many features in common. An increase in ovarian volume and cystic changes in ovaries have been reported in primary hypothyroidism. In the other direction, it is increasingly realized that thyroid disorders are more common in women with PCOS as compared to the normal population[6,7,8,9]. In the presence of hypothyroidism, ovarian morphology becomes poly-cystic. Hence, thyroid disorders are one of the exclusion criteria before making a diagnosis of PCOS in any women. The underlying pathophysiology has been outlined in Figure 1 . Rise in thyrotropin-releasing hormone (TRH) in primary hypothyroidism leads to increased prolactin and thyroid stimulating hormone (TSH). Prolactin contributes toward polycystic ovarian morphology by inhibiting ovulation as a result of the change in the ratio of follicle stimulating hormone (FSH) and luteinizing hormone and increased dehydroepiandrosterone from the adrenal gland. Increased TSH also contributes due to its spill-over effect on FSH receptors. Increased collagen deposition in ovaries as a result of hypothyroidism has also been suggested.

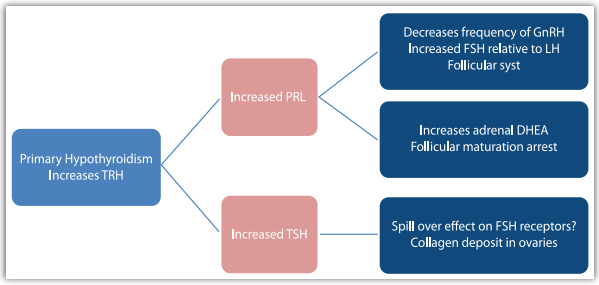

Figure 1: Pathophysiology of polycystic ovaries in patients with primary hypothyroidism

In most severe cases like long standing untreated cases of congenital hypothyroidism ovarian morphology can be very striking and can even be mistaken for ovarian malignancies. These cases have been given an eponym Van Wyk and Grumbach syndrome, after the scientist who first described the case[10]. In a study, on somewhat less severe primary hypothyroidism, by Muderris et al . treatment naïve females with primary hypothyroidism, with mean TSH 57.1 mcg/dl, underwent evaluation of ovarian volume before and after replacement with thyroxine[11]. Recently, in a study by Ganie et al . 175 girls with euthyroid chronic lymphocytic thyroiditis (CLT) and 46 age-matched non-CLT girls underwent evaluation for diagnosis of PCOS[12]. The prevalence of subclinical thyroid dysfunction in the general population has been estimated around 10%, but in reproductive years this prevalence is considerably low at 4-6%[13,14]. The pathophysiological pathway connecting these two disorders has not been clearly delineated as of now. The most obvious connection, perhaps, is the increased BMI and insulin resistance common to both conditions. Increase in BMI is an integral part of PCOS and is seen in a large majority (54-68%) of these cases[15]. The link between thyroid functions and obesity is again an interesting one, with unclear pathophysiological mechanisms; there is, however, enough evidence to say that TSH is higher in people with high BMI[16,17].

Conclusion :

All women with PCOS should have their thyroids evaluated thoroughly (TSH, FT3, FT4, Anti TPO, Anti TG). Thyroid health has a profound impact on the pathology of PCOS, affecting all aspects of the disorder. The polycystic ovary appearance completely disappeared when thyroid function was restored.

Recommendation : Thanks to all the members of infertility family of Mfstc & 100 beded MCH hospital, aurangazeb road, mohammadpur Dhaka for their cordial support. We are so grateful to our honorable Director of this hospital for giving us the opportunity to servicing the infertile couple of this hospital.

References :

1. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18:774-800.

2. Mueller A, Schöfl C, Dittrich R, Cupisti S, Oppelt PG, Schild RL, Beckmann MW, Häberle L. Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod. 2009 Nov;24(11):2924-30.

3. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol. 2004 Mar;150(3):363-9.

4. NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease. Laurence M. Demers, Ph.D., F.A.C.B.and Carole A. Spencer Ph.D., F.A.C.B.

5. Dittrich R, Kajaia N, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Association of thyroid-stimulating hormone with insulin resistance and androgen parameters in women with PCOS. Reprod Biomed Online. 2009 Sep;19(3):319-25.

6. Sinha U, Sinharay K, Saha S, Longkumer TA, Baul SN, Pal SK. Thyroid disorders in polycystic ovarian syndrome subjects: A tertiary hospital based cross-sectional study from Eastern India. Indian J Endocrinol Metab. 2013;17:304–9. [PMC free article] [PubMed]

7. Benetti-Pinto CL, Berini Piccolo VR, Garmes HM, Teatin Juliato CR. Subclinical hypothyroidism in young women with polycystic ovary syndrome: An analysis of clinical, hormonal, and metabolic parameters. Fertil Steril. 2013;99:588–92.[PubMed]

8. Ramanand SJ, Ghongane BB, Ramanand JB, Patwardhan MH, Ghanghas RR, Jain SS. Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocrinol Metab. 2013;17:138–45. [PMC free article] [PubMed]

9. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol. 2004;150:363–9.[PubMed]

10. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap in pituitary feedback. J Pediatr. 1960;57:416–35.

11. Muderris II, Boztosun A, Oner G, Bayram F. Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism. Ann Saudi Med. 2011;31:145–51. [PMC free article] [PubMed]

12. Ganie MA, Marwaha RK, Aggarwal R, Singh S. High prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: A case-control study. Eur J Endocrinol. 2010;162:1117–22. [PubMed]

13. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34. [PubMed]

14. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III) J Clin Endocrinol Metab. 2002;87:489–99. [PubMed]

15. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update. 2012;18:618–37. [PubMed]

16. Asvold BO, Bjøro T, Vatten LJ. Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metab. 2009;94:5023–7. [PubMed]

17. Muscogiuri G, Sorice GP, Mezza T, Prioletta A, Lassandro AP, Pirronti T, et al. High-normal TSH values in obesity: Is it insulin resistance or adipose tissue's guilt? Obesity (Silver Spring) 2013;21:101–6. [PubMed]

Paloxi

Palonosetron INN 0.5 mg tab, 0.075 mg/1.5 ml & 0.25 mg/5 ml IV inj

Power over EMESIS

Comparison of Paloxi and Ondansetron

Feature	Paloxi	Ondansetron	Advantage of Paloxi
Anti-emetic	Highly potent	Relatively potent	100 times more potent hence more effective
Receptor binding	High affinity (30 times more than Ondansetron), allosteric, positive co-operative	5-HT3 receptor blockade, mimics	Long term effect on receptor
Plasma half-life	40 h	4 h	Longer duration of action
Metabolism and drug interactions	Mainly by CYP2D6	Mainly by CYP3A4 isoenzyme	Minimal risk of adverse drug Interactions
PONV and PDNV	Effective	May not be effective with single dosage	Better drug of choice

So, Paloxi is the most safe & effective antiemetic drug

Stop Vomiting

BEACON®
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Light for life

Xalcort

Deflazacort INN 6 mg, 24 mg Tablet & 6 mg/5 ml Suspension

The safer corticosteroid for inflammatory conditions

Better & Safer than Prednisolone

- Zero mineralocorticoid activity
- Less chance of osteoporosis
- Less effect on blood glucose level
- Less chance of growth retardation in children
- Less chance of HPA-axis suppression

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