

**Chief Editor:**  
Ahmad Husari

**Ethics Editor and Publisher:**  
Ms Lesley Pocock  
medi+WORLD International  
Email:  
lesleypocock@mediworld.com.au

**Editorial enquiries:**  
editor@me-jim.com

**Advertising enquiries:**  
lesleypocock@mediworld.com.au

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## 2 Editorial

*Ahmad Husari*  
DOI: 10.5742/ MEIM.2017.92934

## Original Contribution / Clinical Investigation

3 Anthracycline versus Non- anthracycline Induction Regimens in Patients with De Novo Acute Myeloid Leukemia  
*Ashraf Alyamany, Nashwa M Abdel- Aziz, Safaa A. A. Khaled Rabab Farghaly, Ashraf Z. Abd Allah*  
DOI: 10.5742/ MEIM.2017.92935

12 Diffuse peritoneal decidualis in pregnancy: A case report  
*Nansi Al Fayez, Basel Khreisat*  
DOI: 10.5742/ MEIM.2017.92936

16 Diagnosis of Porphyria after sternotomy for severe calcific coronary artery disease, a Case Report  
*Fuad Alazzam, Salah Altarabsheh, Mohammad Khasawneh*  
DOI: 10.5742/ MEIM.2017.92937

19 Quadruplet Heterotopic Pregnancy: a Case Report  
*Rema Khlaif Omosh, Iman Abdulla Fayez, Nancy Dari Alfayez, Manar Mohammad Abu Karaki*  
DOI: 10.5742/ MEIM.2017.92938

22 Assisted Vaginal Deliveries in Far South of Jordan  
*Mitri Rashed, Areej Bisharat, Bassam Nusair, Majida Al-Sukkar, Najwa Al-Sunna*  
DOI: 10.5742/ MEIM.2017.92939

## Community Care

27 White coat hypertension may be an initial sign of an accelerated atherosclerotic process  
*Mehmet Rami Helyaci, Orhan Ayyildiz, Orhan Ekrem Muftuoglu Mustafa Yaprak, Abdulrazak Abyad, Lesley Pocock*  
DOI: 10.5742/ MEIM.2017.92940

# From the Editor



Ahmad Husari (*Chief Editor*)  
Email: editor@me-jim.com

This is the second issue this year that is rich with papers from the region. A paper from Egypt looked into Anthracycline versus Non-anthracycline Induction Regimens in Patients with De Novo Acute Myeloid Leukemia. A total of 90 AML patients were enrolled in the study; they were retrospectively recruited from AML patients who were admitted at South Egypt Cancer Institute (SECI) from 2000-2010. Demographic, clinical, hematologic and data concerning treatment and therapeutic response were collected from hospital records of patients. Results: Analysis of the collected data showed lower median age of the study participants compared to other studies, FAB M2, M3, M4, followed by M1 were the commonest FAB subtypes among the study patients. Survival analysis showed longer overall survival (OS) and progression free survival (PFS) in those treated with anthracycline induction regimens compared with the non-anthracycline treated group. Also, higher incidence of relapse was observed in the non-anthracycline group. Conclusion: Anthracycline based induction regimens are still more effective than non-anthracycline regimens for treatment of AML, however the search for safer drugs than anthracyclines is still mandatory.

A paper from Turkey looked at the role of white coat hypertension (WCH) is unknown in metabolic syndrome. The study was performed in Internal Medicine Polyclinic. The study included 1,068 patients (628 females). Prevalence of excess weight increased from the third (28.7%) up to the seventh decades (87.0%), gradually ( $p < 0.05$  nearly in all steps), and then decreased in the eighth decade of life (78.5%,  $p < 0.05$ ). The most significant increase was detected during the passage from the third to the fourth decades (28.7% versus 63.6%,  $p < 0.001$ ) parallel to the smoking. On the other hand, hypertension (HT), type 2 diabetes mellitus (DM), and coronary heart disease (CHD) always increased without any decrease by decades ( $p < 0.05$  nearly in all steps) indicating their irreversible properties. The authors concluded that probably metabolic syndrome is an accelerated atherosclerotic process all over the body. WCH may be an initial sign of the accelerated atherosclerotic process that can be detected easily.

A case report from Jordan report on Diffuse peritoneal decidu-

osis in pregnancy. The authors stressed that Deciduositis or ectopic decida is the presence of group of decidual cells outside the endometrium. Walker was the first to define the condition in 1887(1). In pregnancy, the occurrence of ectopic deciduas was observed in ovaries, uterus and tubes, while localization in peritoneum was rare. The authors are reporting a case of ectopic deciduas in a 27-year-old lady who was asymptomatic during the course of her pregnancy, presented with preterm labour pain, underwent caesarean section due to Triplet pregnancy. The lesions were discovered accidentally, they were nodular covering most of the peritoneum and there was omental cake, biopsies were taken to differentiate it from malignant conditions. Histopathological diagnosis confirmed deciduositis.

A paper from Oman looked at the Diagnosis of Porphyria after sternotomy for severe calcific coronary artery disease through a case. Acute intermittent porphyria (AIP) is an autosomal disorder marked by a deficiency of the enzyme, the hydroxymethylbilane synthase which is part of the heme biosynthesis. It is manifested clinically by multi-system involvement. Our patient does have chronic ischemic heart disease needed surgical revascularization, his sternotomy incision revealed the classical blackish discoloration of the bone marrow, which guided us for his work up and diagnosis

Another topic that was dealt with from Jordan was Heterotropic pregnancy is a condition in which pregnancy occurs synchronously intrauterine and extrauterine. The estimated incidence following spontaneous conception is below 1/30,000. The authors report a case of a 20 years old woman, nulliparous, who presented to the emergency department with acute abdominal pain post ovulation induction with human menopausal gonadotrophins and intrauterine insemination. Examination revealed acute surgical abdomen. Ultra-sonographic examination showed viable triplet intrauterine gestation of 10 weeks and presence of right complex adnexial mass. Laparotomy done and patient found to have right tubal ectopic pregnancy that was managed by salpingostomy. Though the incidence of heterotropic pregnancy is low following spontaneous pregnancy but a high index of suspicion must be considered in any patient with intrauterine pregnancy who presented with abdominal pain and adnexial mass and particularly if conception occurs after artificial reproductive techniques. This approach would avoid maternal morbidity and mortality.

One more retrospective observational study from South Jordan has been carried out over a four-year period between 1st January 2012 & 31st December 2015. The medical records of all patients who underwent instrumental deliveries were reviewed & analyzed. During this four-year period 238 successful instrumental deliveries were performed out of 9767 deliveries with a rate of 2.56%. The commonest instrument used was vacuum (202/240) and 36 patients were delivered by forceps. The indications were; presumed fetal distress (132), prolonged 2nd stage of labor (85) and maternal exhaustion (21). Maternal complications reported were postpartum hemorrhage (18) and different degrees of genital tract tears (28). Fetal complications registered consisted of 34 cases of which (11) were cases of Erbs palsy, (12) were cases admitted to NICU for observation & one case was diagnosed with cereberal palsy. The authors concluded that their study showed a lower rate of operative vaginal delivery in comparison to the international figures. This may be attributed to the lack of epidural anesthesia; which increases the incidence of instrumental deliveries, in addition to the simple experience of the attending residents who fear of possible complications of applying these instruments and the potential subsequent litigations. The complications reported in our study were expected in assisted vaginal deliveries and mimic those mentioned in the literature.

# Anthracycline versus Non-anthracycline Induction Regimens in Patients with De Novo Acute Myeloid Leukemia

Ashraf Alyamany (1)  
Nashwa M Abdel- Aziz (1)  
Safaa A. A. Khaled (2)  
Rabab Farghaly (1)  
Ashraf Z. Abd Allah (3)

(1) Department of Medical Oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

(2) Department of Internal Medicine, Clinical Hematology Unit, Assiut University Hospital, Faculty of Medicine, Assiut University, Egypt.

(3) Department of Clinical Oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

## Correspondence:

Dr. Safaa A.A. Khaled  
Department of Internal Medicine,  
Clinical Hematology Unit, Assiut University Hospital,  
Faculty of Medicine, Assiut University,  
Assiut, Egypt.

**Email:** sfaakhaled2003@gmail.com

## ABSTRACT

**Background & Objectives:** Acute myeloid leukemia (AML) is the most prevalent form of acute leukemias in adults; unfortunately it carries very poor prognosis. Over the past decade marvelous advances were achieved in understanding pathophysiology of AML and this was reflected in management of AML patients. Nevertheless the standard anthracycline based induction regimens remained the cornerstone for treatment of AML; however their effectiveness is limited by their well known cardiotoxicity. To our knowledge this is the first study that investigated anthracycline versus non-anthracycline induction regimens in patients with AML.

**Methods:** 90- AML patients were enrolled in the study; they were retrospectively recruited from AML patients who were admitted at South Egypt Cancer Institute (SECI) from 2000-2010. Demographic, clinical, hematologic and data concerning treatment and therapeutic response were collected from hospital records of patients.

**Results:** Analysis of the collected data showed lower median age of the study participants compared to other studies, FAB M2, M3, M4, followed by M1 were the commonest FAB subtypes among the study patients. Survival analysis showed longer overall survival (OS) and progression free survival (PFS) in those treated with anthracycline induction regimens compared with the non-anthracycline treated group. Also, higher incidence of relapse was observed in the non-anthracycline group.

**Conclusion:** Anthracycline based induction regimens are still more effective than non-anthracycline regimens for treatment of AML, however the search for safer drugs than anthracyclines is still mandatory.

**Key words:** AML, anthracycline, non-anthracycline.

## 1. Introduction

AML is a hematopoietic stem cell disorder with devastating consequences; it has the lowest survival rate of all leukemias. (1, 2) Unfortunately, AML is the commonest acute leukemia in adults with an incidence of 2.7 per 100,000 persons, (3, 4) with increasing prevalence in the population older than 60 years of age and a median age at presentation of 65 years. (5) Worldwide, the incidence of AML is highest in the U.S., Australia, and Western Europe. (6)

Despite the remarkable advances in treatment of AML, anthracycline based induction regimens have remained the standard therapy in AMLs for more than 40-years. (7, 8) However the well known anthracycline induced cardiotoxicity limits its use in first induction in elderly patients and in those with left ventricular dysfunction. Furthermore its use in re-induction is restricted with the maximum cumulative dose over lifetime. (9)

Anthracyclines are a group of antineoplastic drugs that were first introduced in treatment of AML in 1960; daunorubicin was the first discovered and introduced anthracycline. The complete remission rates (CR) of daunorubicin based induction regimens in AML ranged from 59% - 72% in those under 60-years old; this declined to 31%-45% in those over 60-years old. (10-12) The efficacy of anthracycline was found to be dose dependent, (13- 15) nevertheless their complications are dose dependent too. (16, 17) These facts led to the emergence of non-anthracycline based induction regimens for patients with AML. The combination of fludarabine, Ara-C, and G-CSF was found to induce remission in 58% of AML patients aged  $\geq$  60 years, after first induction. (18) Furthermore, low-dose cytarabine was used and shown to be effective and standard in elderly AML patients. (19)

OS and PFS were used by many researchers to assess the appropriateness and efficacy of drugs used in AML. (20, 21) This study was conducted to assess the anthracycline versus the non-anthracycline based induction regimens in AML patients using OS and PFS.

## 2. Subject and Methods

### 2.1. Study population and data collection

A retrospective study was conducted at SECI, Assiut University, Assiut, Egypt. SECI is a big tertiary health care center that offers superspecialist health care to residents of nearly eight governorates of Egypt. These include, from north to south, Al Menia, Assiut, Sohage Qena, Luxor, Aswan, Al- wady Al -Jadid, and Red Sea Governorates.

Data were collected from hospital records of AML patients who were admitted at SECI in the period 2000 to 2010. Only patients with de novo AML were included in the study; however records with incomplete follow up data were excluded from the study. Both hand written and computer based hospital records were reviewed. Demographic, clinical, and hematologic data were collected; also information about treatments and treatment responses were gathered; outcome of patients was collected too. Both the anthracycline and non-anthracycline groups were matched in sex, age ( $\pm$ 6 years) and residency.

The Eastern Cooperative Oncology Group criteria (ECOG) were used to assess how AML affected the daily life activities of the patients. Data on the ECOG Performance status of patients was recorded. The status was scaled and graded on a 5-point scale as following:

**Table 1: Grades of ECOG performance status. (22)**

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

N.B. ECOG: Eastern Cooperative Oncology Group

## 2.2. Diagnosis of AML in the study patients

Diagnosis of AML in our patients was dependent on clinical suspicion and laboratory certainty. The latter was accomplished with complete blood picture (C.B.C) and bone marrow examination. According to WHO recommendations blast percent of 20% or more were required for diagnosis of AML. (23) Morphological, cytochemical and immunophenotypic examination of neoplastic cells were also performed.

## 2.3. Treatment of AML in the study patients

Before treatment with chemotherapy thorough clinical and laboratory investigations were performed including LFT, KFT, serum electrolytes and blood glucose, also ECG and CXR. Echocardiography was done in those at risk of cardiac dysfunction e.g. hypertension, history of cardiac disease, obesity, smoking, over 40-years old, or previous anthracycline induction. Patients received induction regimens under umbrella of good supportive care in the form of red blood cells and platelet transfusions, broad spectrum antibiotics and antifungals. Neutropenic patients were managed at the Intensive Care Unit. Those with leucocytosis > 100 underwent one setting of leucopheresis before induction. Allopurinol was administered to patients to guard against development of tumor lysis syndrome.

The choice of anthracycline or non-anthracycline based induction regimens was dependent on the possible development of cardiotoxicity. Accordingly non- anthracycline induction was prescribed as first induction in patients with left ventricular ejection fraction < 50% or for re-induction in those with maximum cumulative anthracycline dose > 100%. The latter was calculated as the total anthracycline dose received. The maximum cumulative anthracycline dose for different types of anthracycline drugs was for daunorubicin (500-600 mg/m<sup>2</sup>), doxorubicin ( 450-550 mg/m<sup>2</sup>), idarubicin (93 mg/m<sup>2</sup>), epirubicin (950 mg/m<sup>2</sup>), and (160 mg/m<sup>2</sup>) for mitoxantrone.(24, 25) Those who received anthracycline based regimens were treated with adriamycine (doxorubicin) 25 mg/m<sup>2</sup> per day for 3-days and Ara C 100mg/m<sup>2</sup> per day for 7-days by continuous Infusion. The FLAG or Low dose Ara-C regimens were prescribed for those who received non-anthracycline induction. The FLAG regimen was in the form of Fludarabine 30 mg/m<sup>2</sup> a day IV infusion over 30 minutes, every 12 hours in 2 divided doses on days from 1-5, Ara-C 2000 mg/m<sup>2</sup> IV infusion over 4 hours, every 12 hours in 2 divided doses, starting 4 hours after the end of fludarabine infusion on days from 1-5, and G-CSF 5 µg/kg SC from day 6 till neutrophil recovery. Those who received low dose Ara-C were treated with 20 mg/m<sup>2</sup> cytarabine S.C. /12 hours, four days a week. Another dose was repeated after remission or whenever needed. (26- 28)

## 2.4. Assessment of response to treatment

Bone marrow aspirates or biopsies were performed after one week of induction. Response to treatment was defined according to the criteria developed by the International Working Group.(29) Thus CR was identified by independence from RBCs transfusion, absence of extramedullary disease and platelet & neutrophil counts >100.000/ul & >1000/ul, respectively. Bone marrow aspiration or biopsy reveals <5% blast with absence of Auer rods and normal maturation of all cel-

lular elements of blood were also needed to define CR. On the other hand Partial response was defined as normal CBC and >50% decline of bone marrow blasts. If patient developed complications either of the disease or the treatment he/she was categorized in the group of complicated disease. Disease free survival was considered as the time from when the patient is rendered free of clinically detectable cancer until recurrent cancer is diagnosed.

Progression free survival was estimated as the time from the start of treatment to the first documentation of objective tumor progression or death as a result of any cause. Date of mortality was assessed to calculate the overall survival, which is the time from start of study treatment to date of death as a result of any cause.

## 2.5. Statistical analyses

The collected data were verified, coded by the researcher and analyzed by using the Statistical Package for Social Sciences (SPSS/PC/VER 17). Follow up data of AML patients attending SECI from 2000 to 2010 were also analyzed. Descriptive statistics, mean, standard deviation, and frequencies, were calculated. Test of significances Chi square test was used to compare the difference in distribution of frequencies of remission and relapse in the two induction groups. Kaplan-Mayer and Survival analysis was calculated. Significant test results were considered when p value was < 0.05.

## 2.6. Ethical considerations

The study design, objectives and methods were consistent with both the declaration of Helsinki and the guidelines of the research ethical committee at SECI. Furthermore, agreement of the Vice Dean of SECI was obtained before handling patients' records.

## Results

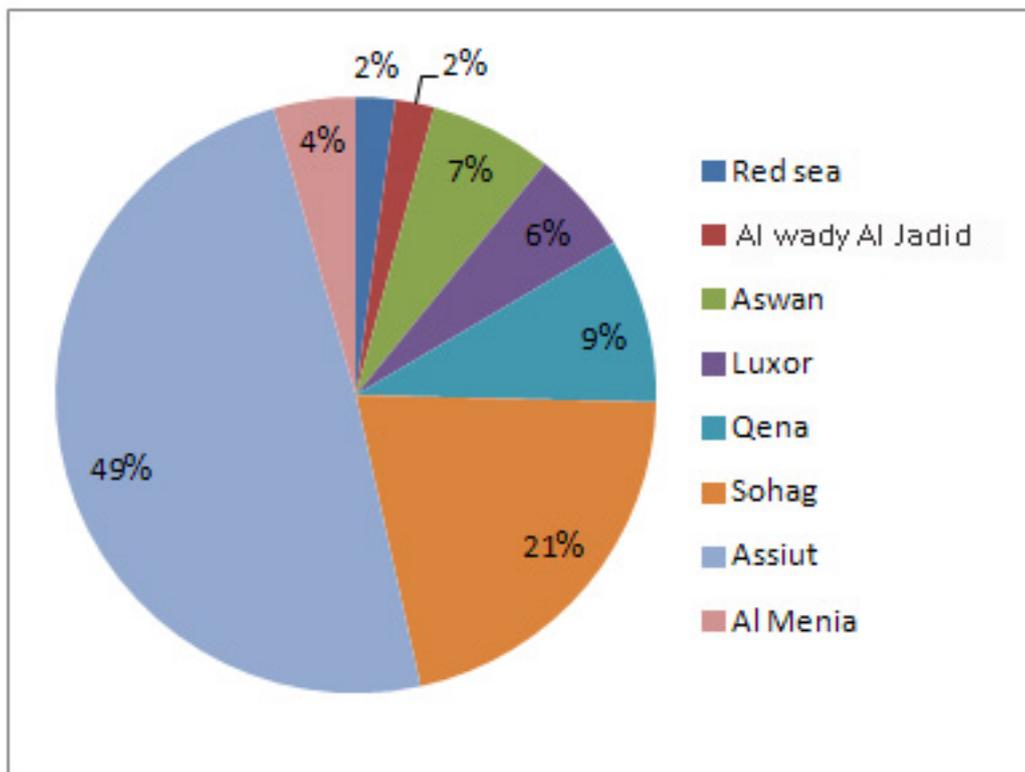
### 3.1. Characteristics of the study participants

A total of 90 AML patients were enrolled in the study; their mean age was 37.9 ± 6.9 and 51.1% were males, with a male to female ratio 1.04:1. The vast majority of the studied group was from Assiut governorate (44%) while the least frequency was from both Red Sea and Al- wadi Al- Jadid governorates (1%) and Figure 1 shows the distribution of the study group over governorates of Upper Egypt. Their ECOG performance status ranged from 1-2. Marked leukocytosis was observed in 4 (4.4%) of patients where their total Leukocytic count was >100,000. Only 5(5.6%) patients had CNS infiltration. As we are interested in determining the efficacy of anthracyclines we classified regimens used to two groups; the first group includes regimens which contain anthracyclines (n=74), while the second group is without anthracyclines (n= 16). Response to treatment was non remission in 28 patients (31.1%) and 62 patients achieved remission after induction chemotherapy (68.9%), as depicted in Table 2.

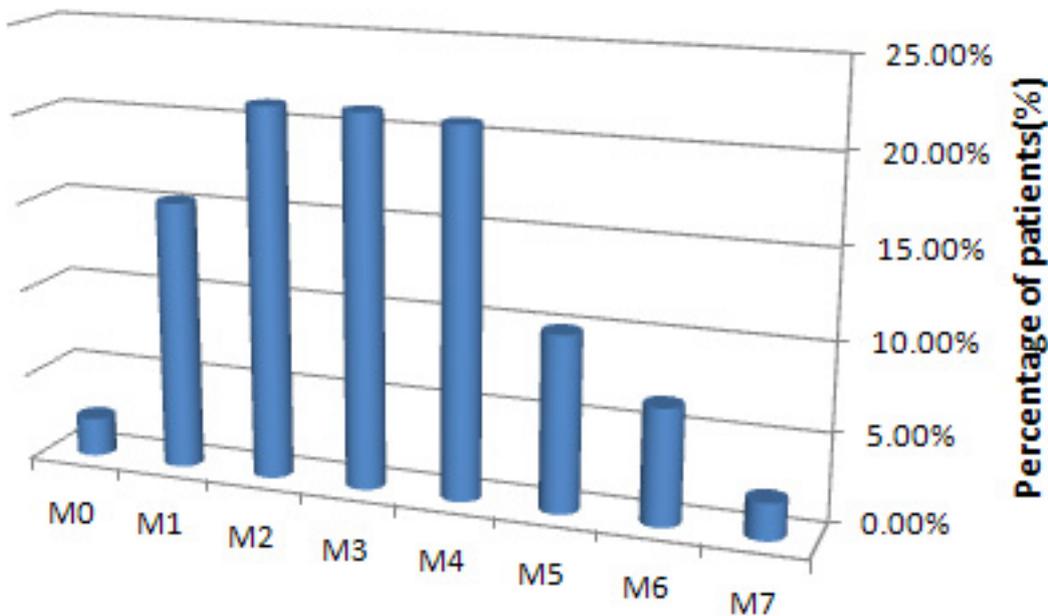
Table 2: Characteristics of the study participants (n=90).

Variable	Category	Frequency (%)
Age (Mean $\pm$ SD)		<b>37.9 <math>\pm</math> 6.9</b>
Sex	Male	46 (51.1%)
	Female	44 (48.9%)
Performance State	1	76 (84.4%)
	2	14 (15.6%)
Total Leukocytic Count	< 100.000	86 (95.6%)
	> 100.000	4 (4.4%)
CNS infiltration	No	85 (94.4%)
	Yes	<b>5</b> (5.6%)
Regimens used for induction	Anthracycline	74(82.2%)
	Non-anthracycline	16(17.8%)
Response to treatment	Remission	62 (68.9%)
	No Remission	28 (31.1%)

Figure 1: Distribution of AML patients over 8 governorates of Egypt



Patients had different FAB subtypes; however M2 and M3, M4 followed by M1 were the most frequent subtypes among the study group, 21.1% and 17.8%, respectively. In the hospital records of 7.8% of AML patients' data about AML type was missing. Figure 2 shows AML FAB subtypes in the study group.



**Figure 2. AML FAB subtypes of the study patients.**

### 3.2. Survival Analysis of Anthracycline vs non-anthracycline treated patients

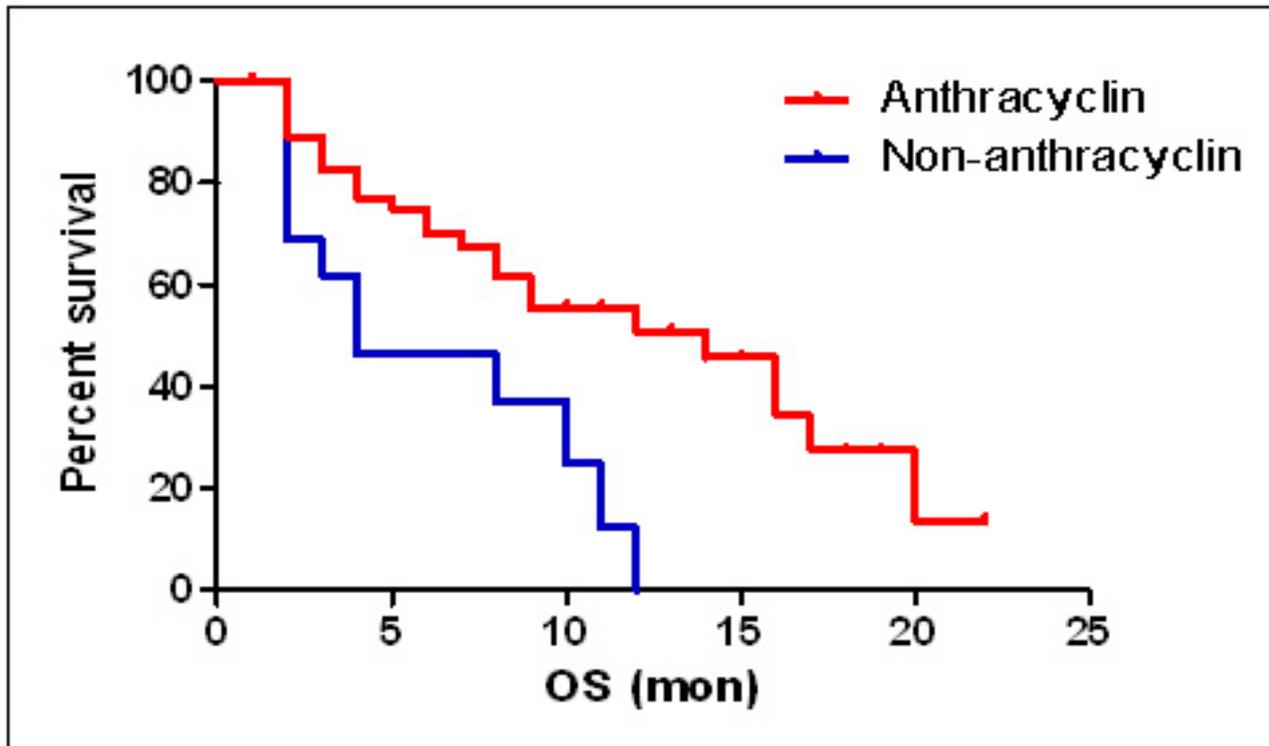
#### 3.2.1. Overall survival:

When we compared survival and response between treatment groups, we found that the anthracycline group showed better survival than the other group which was statistically highly significant ( $p$  value =0.0022), as in Table 3 and Figure 3 .

**Table 3: Overall survival of Anthracycline treated group vs non-anthracycline**

Survival time(months)	No. Exposed to Risk		Survival proportion	
	Anthracycline	Non anthracycline	Anthracycline	Non anthracycline
5	37	8	75%	46.4%
10	17	3	55.4%	24.8%
15	9	0	45.7%	0%
20	2	0	13.7%	0%

Figure 3: Overall survival of Anthracycline treated group vs non anthracycline ( P value was calculated with Log-rank (Mantel-Cox test). \*\*P=0.0022

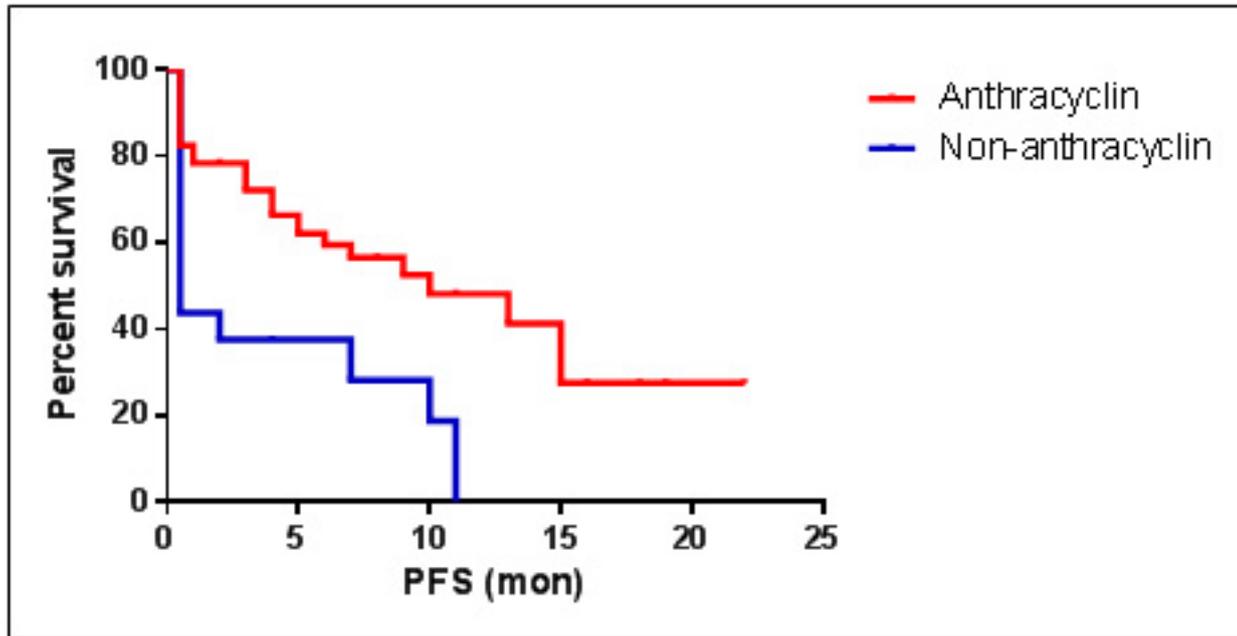


### 3.2.2. Progression free survival:

There was a statistically significant difference between anthracycline and non anthracycline groups (p value =0.0021). Median progression free survival of anthracycline group is 10 months. In non anthracycline group, 13 patients out of 16 suffered from relapse, while the remaining 3 patients showed remission after induction, but didn't continue follow up at our institute as in Table 4 and Figure 4.

Table 4: Progression free survival of Anthracycline treated group vs non-anthracycline.

Survival time(months)	No. Exposed to Risk		Survival proportion	
	Anthracycline	Non anthracycline	Anthracycline	Non anthracycline
5	31	5	62.1%	37.5%
10	12	3	48.1%	18.8%
15	6	0	27.5%	0
22	1	0	27.5%	0

**Figure 4: Progression free survival of Anthracycline treated group vs non anthracycline (\*\*P=0.0021).**

#### 4. Discussion

AML is a hematological malignancy that is characterized by marked clinical and genetic heterogeneity. Over the past 20-years extensive research was conducted in a trial to develop new targeted therapies for AML and improve its prognosis. Nevertheless treatment of non-APL AML is still dependent on the standard 3/7 induction regimen of the anthracycline antibiotic and the cell cycle specific agent cytarabine. CR is obtained in 25%-75% of newly diagnosed patients with this regimen. Cardiotoxicity of anthracycline was found to be dose dependent and limits its use in re-induction. (30-33) This research was conducted to assess the outcome of patients with AML treated with induction regimens containing anthracycline drugs versus those treated with non-anthracycline regimens. The main objective was to prove or disprove the efficacy of non anthracycline drugs in AML in a trial to recommend the inclusion of these agents in first induction.

Acute myeloid leukemia (AML) presents in all ages but is mainly a disease of the elderly with a median age of 69 years in the white US population, but in our study median age was 37 years. The life expectancy of Egyptians is 72 years compared to 78 years for the Americans and almost 95% of the Egyptians are below 60 years compared to 13% for the Americans. (34-36) So usually at SECI the number of young patients is more than the old patients; this may be due to exposure to hazardous chemicals (benzene) or to radiation and it is reported that many of the adult cases with leukemia are cigarette smokers, (37, 38) and usually young adults seek medical advice more than elder ones.

Results of this study reaffirmed previous findings of male predominance in AML and that CNS involvement is uncommon in AML patients. (39, 40) The incidence rate of AML for U.S. males is substantially higher than the incidence rates reported for males in all other countries. The exact significance of this

gender preference is not clear. (41) In our study, the most common FAB subtypes were M2 (21.1%) and M4 (17.8%). This is the same reported with FAB classification in USA and UK, 42 but M3 (21.1%) is also high as SECI is the tertiary referral center which has the facilities to treat this type but the other types can be managed in other centers.

In our country, Adriamycin is the most commonly used anthracycline in induction of remission other than daunorubicin or idarubicin, as it is the more available and cheaper. The last study that reported the use of Adriamycin in treatment of AML was in 1982, comparing the use of Adriamycin (30 mg/m<sup>2</sup>) versus daunorubicin (30 mg/m<sup>2</sup> and 45mg/m<sup>2</sup>). Response rate for Adriamycin was 58% compared to 59% and 72% for daunorubicin. (31) Interestingly, the use of Adriamycin in 3 and 7 regimens in this study achieved remission rate as high as 69%; almost similar to high dose daunorubicin when used for induction of remission in the above mentioned study.

In Yates et al study, (31) they included all AML patients without considering the cytogenetic type or patients' performance, which were later proved to have a strong impact on the response to induction. This probably resulted in including some patients who are expected not to respond well or more prone to toxicity. This is a major confounding factor which may affect the usefulness and the validity of the result. (43) Unfortunately, no other studies tried to re-investigate the use of Adriamycin in a prospective randomized controlled trial to prove or disprove the usefulness of its use in AML. The results reported in this study added more evidence encouraging the use of Adriamycin as a cheaper anthracycline alternative to the more expensive types in 3 and 7 regimens.

The main concern about the use of Adriamycin in the management of AML is higher incidence of toxicity. Based on our experience the dose of Adriamycin routinely used is 25 mg/m<sup>2</sup>. This dose is effective as we reported much less toxic side effects than the ordinary dose (30 mg/m<sup>2</sup>). Recently risk

of Adriamycin toxicity has markedly reduced as many natural antioxidants are proved to prevent Adriamycin toxicity including vitamin E, vitamin C, coenzyme Q, carotenoids, vitamin A, flavonoids, polyphenol, resveratrol, antioxidant from virgin olive oil and selenium. (32)

Low-dose cytarabine is recommended for elderly patients (above 75 years). (43) However in our practice we may use this regimen for younger patients (50 to 75 years old) due to poor performance status and associated co-morbidities which are relatively common among Egyptian patients. Results of the current study showed longer OS and PFS in the anthracycline treated AML patients compared to the non-anthracycline group after fixation of other risk factors e.g. age, ECOG performance status. Furthermore a higher rate of relapse was observed in the non-anthracycline treated group.

In conclusion this study showed that despite the well known toxicity of the anthracycline chemotherapeutics, they still have a superior efficacy compared to the non-anthracycline drugs. Accordingly non-anthracycline drugs could not be recommended for first induction in younger age AML patients. However the search for drugs safer than anthracyclines is mandatory.

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# Diffuse peritoneal decidualosis in pregnancy: A case report

Nansi Al Fayez  
Basel Khreisat

Department of Obstetrics and Gynecology,  
King Hussein Medical Center,  
RMS, Jordan

## Correspondence:

Nansi AlFayez MD  
Department of Obstetrics and Gynecology,  
King Hussein Medical Center,  
RMS, Jordan  
**Email:** nancy\_ghishan@yahoo.com

## Introduction

Deciduosis or ectopic decidua is the presence of a group of decidual cells outside the endometrium. Walker was the first to define the condition in 1887(1). In pregnancy, the occurrence of ectopic deciduas was observed in ovaries, uterus and tubes, while localization in peritoneum was rare(2-6). It is important to differentiate between this benign phenomena and Mesothelioma, malignant carcinoma and metastatic malignant Melanoma(7,8). We are reporting a case of ectopic deciduas in a 27-year-old lady who was asymptomatic during the course of her pregnancy, presented with preterm labour pain, and underwent caesarean section due to Triplet pregnancy. The lesions were discovered accidentally; they were nodular covering most of the peritoneum and there was omental cake. Biopsies were taken to differentiate it from malignant conditions. Histopathological diagnosis confirmed deciduosis.

## Case Presentation

A 30-year-old lady, P0+1, 28 weeks pregnant with triplets, her pregnancy is a product of intrauterine insemination after a few years of secondary infertility. Her pregnancy was smooth till a few hours prior to presentation when she started to complain of labor like abdominal pain; on examination she was found to have 4 cm dilated cervix shortening in its length. She underwent emergency caesarean section, and after closure of the uterus, inspection of abdominal cavity revealed presence of whitish nodules on the tubes, ovaries, meso-colon (picture 1) and extensive nodularity of the omentum forming omental cake. Biopsies were taken from the nodules, and the omentum; they were sent for histopathology. Peritoneal wash was sent for cytology. The immunohistopathology confirmed the diagnosis of ectopic decidua. Eight weeks later the patient underwent diagnostic laparoscopy as follow up; the lesions were resolved completely (pictures 2,3,4).

## Discussion

Extensive peritoneal deciduosis is a rare condition(2-6,9). It is seen in ovaries, uterine serosa, pelvic side wall, bowel and omentum. The macroscopic intraoperative appearance suggests peritoneal carcinomatosis, as we have in our case.(10)

Ectopic deciduas could be seen in the appendix, diaphragm, spleen, liver renal pelvis and paraaortic-pelvic lymph nodes(9,11-14). It has been documented to occur mostly in other sites of Mullerian origin(15-17).

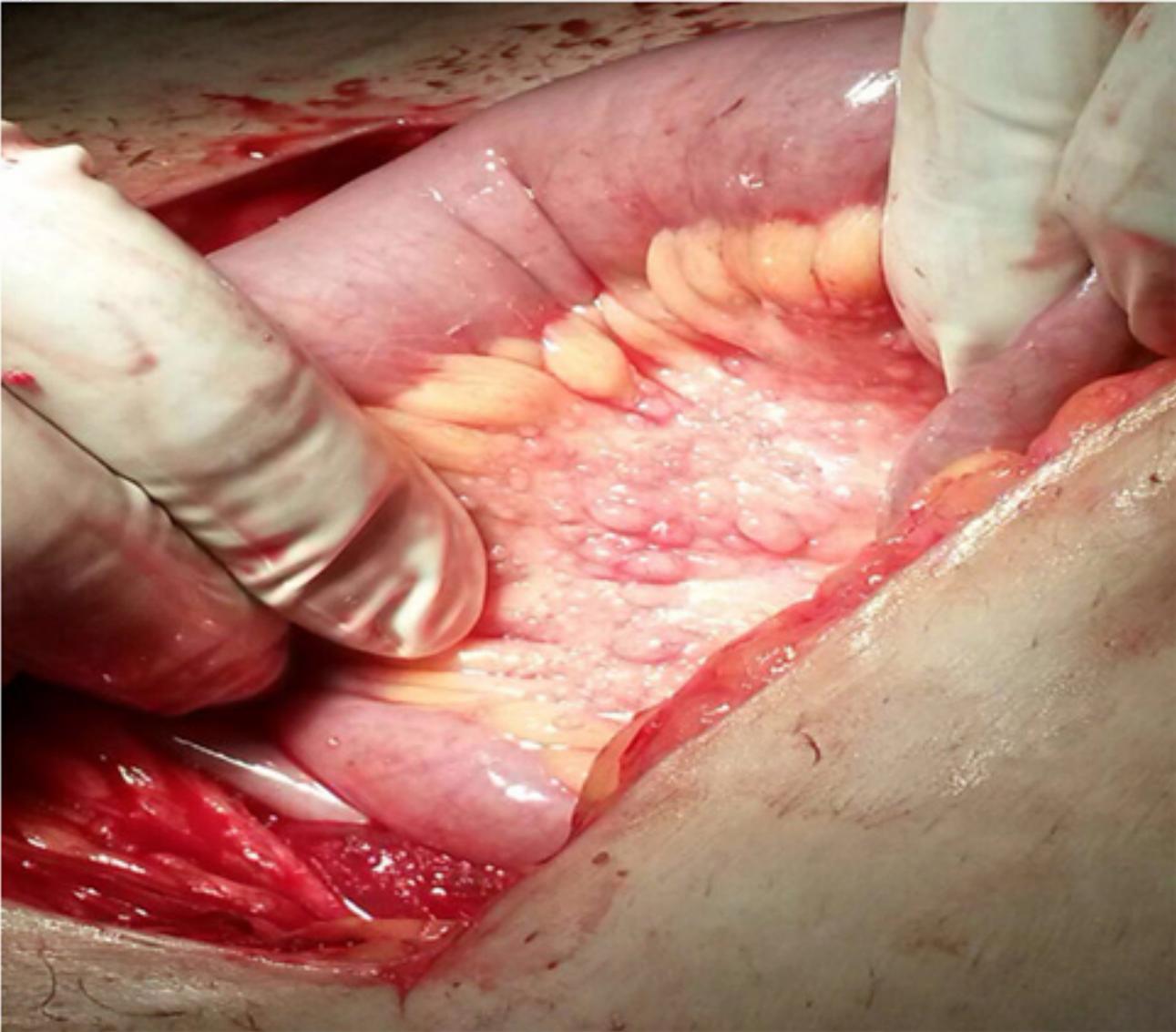
The majority of ectopic deciduas cases has been associated with progesterone secreting corpus luteum in pregnancy(6-8). A diffuse form is uncommon and occurs in the conditions of high levels of progesterone, most commonly seen in pregnant women with multigestation(15-17) as we have in our case. In the absence of pregnancy, the stimulation of ectopic decidual cells attributed to progesterone secreted from adrenal cortex.(7) Deciduosis is usually asymptomatic during pregnancy, and discovered accidentally during caesarean section(18). Cases of pseudo-acute appendicitis, haemoperitoneum, cutaneous swellings and abnormal appearance of cervix have been reported in pregnancy(19,20).

Malpica et al, reported a case of obstructed labour due to gross peritoneal deciduosis in 2002.(21)

The appearance of peritoneal deciduosis ranges from geographic pattern, nodular distribution to polypoid appearance (7-9,16). In our case they were in the form of multiple small nodules.

Diffuse lesions on the omentum are seen on the peritoneal surface as grey-white multiple and presence of focal haemorrhagic nodules or plaques, detected intraoperatively, as we saw in our case. They should be differentiated from peritoneal tuberculosis or metastatic lesions and can be confused in frozen section(6-9,13).

**Figure 1: Diffuse nodularity of meso-colon**



**Figure 2: pelvic side wall 8 weeks post cesarean section**



**Figure 3: pelvic side wall with ovary and tube 8 weeks post cesarean section****Figure 4: pouch of Douglas 8 weeks post cesarean section**

On histopathological examination, it is important to differentiate ectopic deciduas from decidual malignant mesothelioma, metastatic malignant melanoma and vacuolated decidual cells from metastatic signet ring cell carcinoma.

Deciduoid Mesothelioma is a variant of Mesothelioma that can be seen in a wide range of ages, with similar outcome as epithelioid mesothelioma(23,24);the cells are large, with well defined borders, abundant eosinophilic cytoplasm, little pleomorphism, low mitotic activity and cohesive.(23)

Signet ring cell carcinomatosis have cells with eccentric nuclei, mucin filled cytoplasm and diffuse infiltrating cells that can be found in the form of single cells, cords and nests.(25)

The diagnosis of decidual mesothelioma will be supported by positivity of cytokeratin 5/6 and calretinin on immunohistochemical analysis, while the HMB-45 S-100 protein and keratin positivity metastatic carcinoma support malignant melanoma.(26,27) The clinical history, the lack of mitosis in decidual cells, negativity of calretinin, keratin, HMBE-1 and vimentin and PR positivity on immunohistochemical analysis support decidualosis.(8,26,27)

## Conclusion

Deciduosis or ectopic deciduas represents a physiological reaction of pluripotent stromal cells to stimulation of progesterone. It is a benign lesion, and resolves spontaneously in the postpartum period. Nodules should be biopsied during surgery to be differentiated from malignancy.

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# Diagnosis of Porphyria after sternotomy for severe calcific coronary artery disease, a Case Report

Fuad Alazzam (1)  
 Salah Altarabsheh (1)  
 Mohammad Khasawneh (2)

(1) MD, Division of Cardiovascular Surgery, Queen Alia Heart Institute, Amman, Jordan  
 (2) MD, Division of Cardiac Anesthesia, Queen Alia Heart Institute, Amman, Jordan

## Correspondence:

Mohammad Khasawneh, MD  
 Queen Alia Heart Institute  
 Jordanian Royal Medical Services  
**Email:** khasawneh03@yahoo.com

## ABSTRACT

**Acute intermittent porphyria (AIP) is an autosomal disorder marked by a deficiency of the enzyme, the hydroxymethylbilane synthase which is part of the heme biosynthesis. It is manifested clinically by multi-system involvement. Our patient does have chronic ischemic heart disease needed surgical revascularization; his sternotomy incision revealed the classical blackish discoloration of the bone marrow, which guided us for his work up and diagnosis.**

**Key words:** acute intermittent porphyria (AIP), coronary artery bypass grafting (CABG), left internal mammary artery (LIMA).

## Introduction

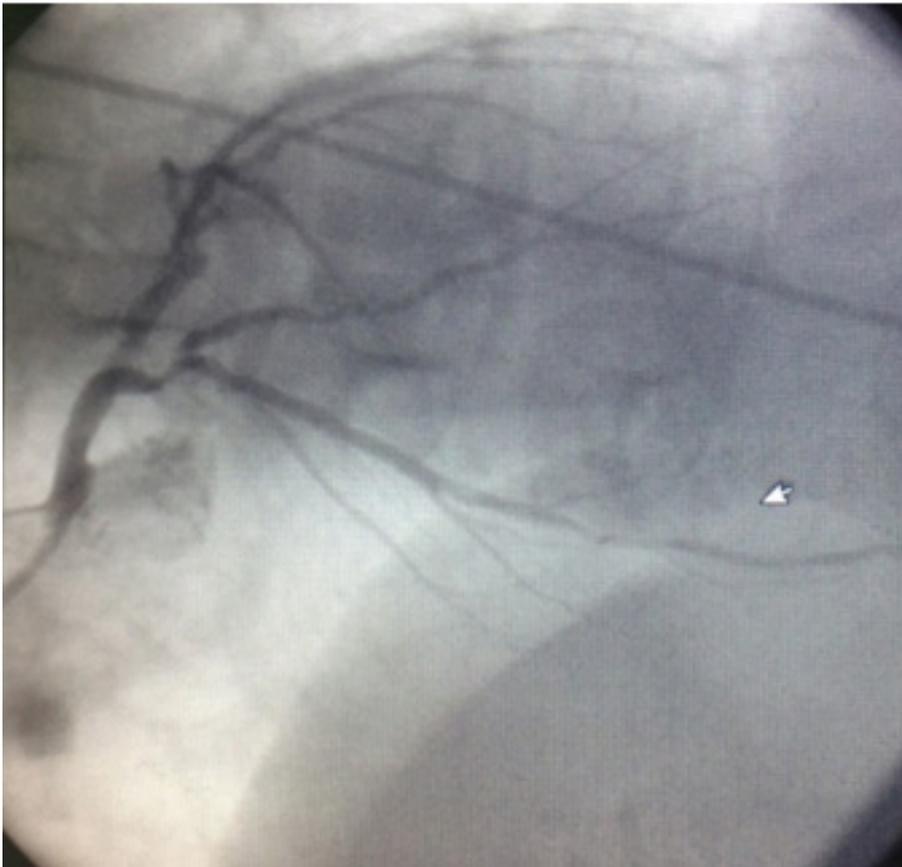
Porphyria, a hematological disease, which involves the heme metabolism, can present with multiple features. It has many clinical presentations which can mimic multiple diseases.

Here we present this case which was diagnosed with acute intermittent porphyria (AIP) during sternotomy for CABG.

## Introduction

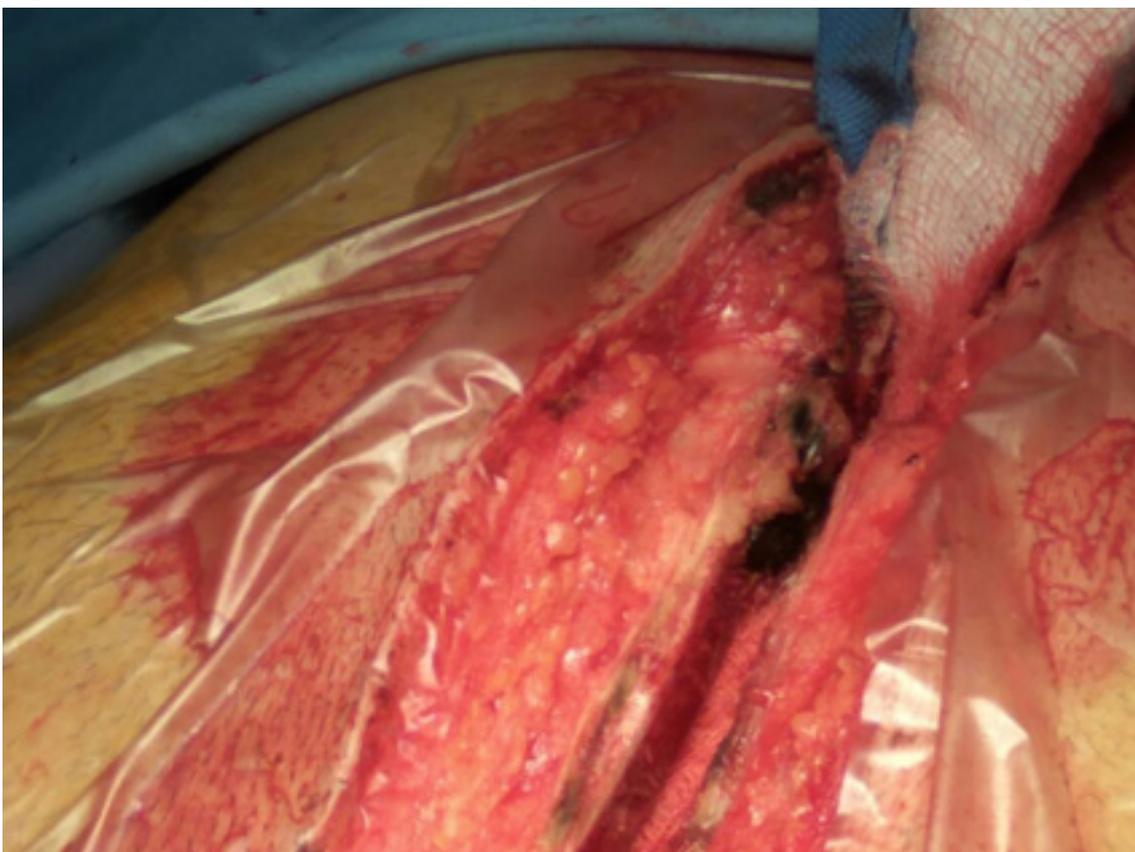
We report a 40-year-old gentleman who, apart from smoking history, had no other risk factors for coronary artery disease. One more pertinent issue is that he had a chronic history of vague left loin pain which is intermittent and was treated as urinary gravels. This gentleman had recurrent attacks of angina chest pain, for which he was studied in the cardiology clinic and his work up included coronary angiogram which revealed three vessel coronary artery disease not amenable for percutaneous coronary intervention. After reviewing his coronary angiogram, there were multiple calcific lesions with variable distribution along his coronary territories (Figure 1). Decision was taken to operate on him and perform coronary artery bypass grafting. He was brought to the operating room for elective triple coronary bypasses for his diseased coronaries. Given his very young age, this raised the suspicion of a systemic disease.

**Figure 1: Coronary Angiogram revealing multiple diffusely distributed calcific spots along the coronary territories.**



After being prepped and draped in the usual sterile fashion, full primary median sternotomy was performed. Interestingly there was a dark black colored bone marrow spot at the distal lower part of the sternum (Figure 2), for which, an incisional biopsy was sent to the histopathology laboratory. During LIMA harvesting, multiple dark black spots covering multiple ribs were also noted.

**Figure 2: Intra-operative view, demonstrating a blackish discolored spot in the lower aspect of the sternotomy incision**



When pericardium was opened and heart suspended in pericardial cradle, cardiopulmonary bypass was commenced at 2.4 L/M/M2 and patient temperature drifted to 34 c. and cardioplegic arrest done with ante grade and retrograde fashion. Coronary arteries were examined and showed diffuse calcification with multiple dark spots.

Surgery was uneventful and patient recovered fully and was discharged 10 days after multiple diagnostic tests were sent and confirmed his disease.

## Discussion

Many groups of disorders that are due to accumulation of Porphyrins can produce the disease of porphyria (1 ,2). It is inherited as autosomal pattern - which is most common - as well as autosomal recessive - rarely occurring Porphyria's affect many organs including CNS, skin, kidneys, liver and bone as well.

Vague presentations and lots of nonspecific signs and symptoms make the diagnosis difficult in solitary cases which have no family history of such a disease, as in this case.

Triggering factors that might precipitate the acute attacks of porphyria include alcohol, smoking, medications, fasting, stressful events, infections and others.

Other forms of porphyria can produce cutaneous manifestations which is not in the scope of this case.

## Conclusion

Subtle changes of organ tissues can be the stepping stone for the workup of rare diseases. High index of suspicion and systemic examinations of all tissues apart from the planned interventions may make outcomes better. Our case can serve as a reminder to keep these rare diagnoses in mind when such a scenario may be faced.

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# Quadruplet Heterotopic Pregnancy: a Case Report

Rema Khlaif Omosh  
Iman Abdulla Fayez  
Nancy Dari Alfayez  
Manar Mohammad Abu Karaki

Royal Medical Services  
Jordan

## Correspondence:

Dr. Rema Khlaif Omosh JBOG  
Royal Medical Services  
Jordan  
Email: remaomosh@yahoo.com

## ABSTRACT

**Background:** Heterotopic pregnancy is a condition in which pregnancy occurs synchronously intrauterine and extrauterine. The estimated incidence following spontaneous conception is below 1/30,000. On the other hand, the incidence in artificial reproductive techniques has been reported to be as high as 1/100.

**Case:** This case report is of a 20 year old woman, nulliparous, who presented to the emergency department with acute abdominal pain post ovulation induction with human menopausal gonadotrophins and intrauterine insemination. Examination revealed acute surgical abdomen. Ultra-sonographic examination showed viable triplet intrauterine gestation of 10 weeks and presence of right complex adnexal mass. Laparotomy was done and the patient was found to have right tubal ectopic pregnancy that was managed by salpingostomy. Post operative period was uneventful and patient was discharged with viable three embryos and she was followed as an outpatient in a high risk pregnancy clinic.

**Comment:** Though the incidence of heterotopic pregnancy is low following spontaneous pregnancy but a high index of suspicion must be considered in any patient with intrauterine pregnancy who presented with abdominal pain and adnexal mass and particularly if conception occurs after artificial reproductive techniques. This approach would avoid maternal morbidity and mortality.

**Key words:** Heterotopic pregnancy, Adnexal mass, Artificial reproductive techniques, Ectopic pregnancy

## Presentation

A 20 year old woman, nulliparous, presented to the emergency room (ER) with a chief complaint of right sided abdominal pain associated with vaginal spotting. She had right sided abdominal discomfort and dull aching pain for the last four weeks, but she developed more intense colicky pain over the last three hours prior to her presentation to the ER.

On history review she was found to have 2 years of infertility and she was followed in our infertility clinic. She was diagnosed as a case of unexplained infertility and accordingly she underwent ovulation induction treatment by human menopausal gonadotrophin (HMG) and intrauterine insemination (IUI). Eventually, she got pregnant and her clinical pregnancy was documented by ultrasonography (US) examination. She was found to have three intrauterine gestational sacs. Folic acid 5mg was prescribed to her since the time of IUI.

At time of presentation to the ER she was 10 weeks pregnant. History was negative regarding previous episodes of the same pain or any previous medical conditions and she had no past history of abdominal surgical procedures. Additionally she had no bowel or urinary symptoms.

## Examination

She was in pain, anxious, had low grade fever and other vital signs were stable. She had generalized lower abdominal tenderness but localized right iliac fossa rebound tenderness. Per vaginal examination showed closed cervix, minimal spotting and mild cervical excitation. US examination showed a viable intrauterine triplet pregnancy with crown rump length of 9 weeks plus 2 days, 9 weeks plus 4 days and 10 weeks. Interestingly, there was a right complex adnexal mass of 7 x 8 cm and minimal free fluid in pouch of Douglas. Her complete blood count (CBC) was normal except for the presence of mild leukocytosis. The patient was admitted to the ward and evaluated by the surgical team who raised the suspicion of appendicular mass.

## Intervention

She underwent laparotomy and was found to have a normal appendix and a right sided intact ampullary ectopic pregnancy and salpingostomy was performed. The left tube and both ovaries were normal.

Care was taken in handling the uterus and the right ovary to avoid any possible damage to the intrauterine pregnancy and particularly not to damage the corpus lutea .

Postoperatively the patient had an uneventful recovery. Ultrasound confirmed the viability of the three fetuses and histopathology confirmed the diagnosis. She was discharged two days after laparotomy and followed as an outpatient. At time of writing this report she is now 23 weeks of gestation and her pregnancy is smooth with regular ante natal care.

## Discussion

Heterotopic pregnancy is defined as the presence of multiple gestations with one being in the uterine cavity and the other outside the uterus, commonly in the tube (Karli 4).

Today there is an increase in the use of artificial reproductive techniques and fertility drugs to improve fertility rate. This raises the patient's risk of having a heterotopic pregnancy due to the combined effect of hyperstimulation and simultaneous transfer of more than one embryo into the uterus (M. Liu 8 ). Other risk factors which are responsible for infertility like PID and previous tubal surgeries also contribute to heterotopic pregnancy ( Luo X. 5) .

Diagnosing heterotopic pregnancy is still a challenge for the obstetricians and many cases are diagnosed very late( Karim IM 7).The diagnostic role of serum B-hcg level in heterotopic pregnancy is debatable . The normal algorithm for the rapid rise in the serum B-hcg in early pregnancy cannot be used due to the presence of the intrauterine gestation which could lead to false assurances ( David K 12 ). Likewise, abdominal and pelvic ultrasound also fails to demonstrate the ectopic component or it is misinterpreted due to the presence of the intrauterine pregnancy (Nnoli 1).

Laparoscopic salpingostomy or salpingectomy is preferred over laparotomy to minimize manipulation of the pregnant uterus . If the hemodynamic status is compromised, laparotomy is the only choice ( Maalt ME 10 ). For an unruptured ectopic pregnancy, systemic methotrexate is contraindicated because of the viable intrauterine pregnancy (Asha Baxi 2).

## Conclusion

As no single investigation can predict the coexisting heterotopic pregnancy , it should be suspected in any pregnant woman in her early weeks of gestation who presents with lower abdominal pain even with a documented intrauterine pregnancy . This is particularly important following fertility treatment.

Demonstration of an intrauterine pregnancy is no longer a reliable indicator for excluding an ectopic pregnancy.

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# Assisted Vaginal Deliveries in Far South of Jordan

Mitri Rashed (1)  
 Areej Bisharat (2)  
 Bassam Nusair (3)  
 Majida Al-Sukkar (4)  
 Najwa Al-Sunna (5)

(1) Mitri Rashed MD JBOG Senior specialist in Obstetrics & Gynaecology Prince Hashem Bin Abd-Allah The Second Military Hospital-Aqaba Jordan.

(2) Areej Bisharat MD JBPN Specialist in Paediatrics & Neonatologist Queen Rania Al-Abdulla children Hospital-Amman Jordan.

(3) Bassam Nusair MD JBOG Senior Specialist in Obstetrics & Gynaecology King Hussein medical centre-Amman Jordan.

(4) Majida Al-Sukkar MD JBOG Specialist in Obstetrics & Gynaecology King Hussein medical centre-Amman Jordan.

(5) Najwa Al-Sunna MD JBPN Senior Specialist in Paediatrics & Neonatologist, Queen Rania Al-Abdulla children Hospital-Amman Jordan.

## Correspondence:

Mitri Rashed MD JBOG  
 Senior specialist in Obstetrics & Gynaecology  
 Prince Hashem Bin Abd-Allah The Second Military Hospital-Aqaba  
 Jordan  
**Email:** mitrirashed@yahoo.co.uk

## ABSTRACT

**Objective:** To determine the rate, indications and complications of instrumental deliveries at Prince Hashim Ben Abdullah The Second Hospital (former name Princess Haya Bent Al-Hussein), Aqaba, Jordan.

**Methods:** This retrospective observational study has been carried out over a four-year period between 1st January 2012 and 31st December 2015. The medical records of all patients who underwent instrumental deliveries were reviewed and analyzed.

**Results:** During this four-year period 238 successful instrumental deliveries were performed out of 9,767 deliveries with a rate of 2.56%. The commonest instrument used was vacuum (202/240) and 36 patients were delivered by forceps. The indications were; presumed fetal distress (132), prolonged 2nd stage of labor (85) and maternal exhaustion (21). Maternal complications reported were postpartum hemorrhage

(18) and different degrees of genital tract tears (28). Fetal complications registered consisted of 34 cases of which (11) were cases of Erbs palsy, (12) were cases admitted to NICU for observation and one case was diagnosed with cerebral palsy.

**Conclusion:** Our study showed a lower rate of operative vaginal delivery in comparison to the international figures. This may be attributed to the lack of epidural anesthesia which increases the incidence of instrumental deliveries, in addition to the simple experience of the attending residents who fear possible complications of applying these instruments and the potential subsequent litigation. The complications reported in our study were expected in assisted vaginal deliveries (AVD) and mimic those mentioned in the literature.

**Key words:** instrumental deliveries, indications, complications, Jordan

## Conclusion

Assisted vaginal delivery offers the option of an operative procedure to safely and quickly remove the infant, and to safeguard mother and obstetrician from a difficult or even hazardous situation when spontaneous vaginal delivery does not occur within a reasonable time. A successful assisted or operative vaginal delivery trial avoids caesarian section with its attendant uterine scar and implications for future pregnancies. It also avoids potential birth asphyxia from prolonged fetal and cord compression. Reviews of delivery statistics showed considerable variation in the incidence of assisted vaginal deliveries, but the range is usually between 10% and 20% of all deliveries (1, 2). Whether the method employed is the ventouse (vacuum extractor) or the obstetrics forceps, the operator can expect optimal results only when careful attention is given to the indications, prerequisites and performance of the procedure.

## Methods

This retrospective observational study included all pregnant ladies booked in the antenatal clinic and unbooked patients admitted in early labor for whom assisted vaginal delivery was indicated later. It also included all those cases coming in to the emergency room at any time for whom assisted vaginal delivery was indicated.

The medical records of all patients and their babies who underwent AVD at Prince Hashem Ben Abdullah The Second hospital between 1st of January 2012 and 31st of December 2015 were reviewed and analyzed.

The age, parity and the indication for the AVD were recorded. The decision to undertake an AVD was in every case made by

the obstetrician in charge. The procedure was performed by the specialist or by attending resident. All AVDs were performed using either metallic cup (Malstrom or Birds) or obstetrician forceps (long and short Simpson or Wrigly's). The prerequisites of application are mentioned in (Table 1) (2). Either Foley catheter or prostin vaginal tablets (dinoprostone 3mg) or both were used for induction of labor in indicated cases. Artificial rupture of membranes or oxytocin or both were used for augmentation of labor. Pethidine was the main analgesic given in the 1st stage of labor, and local analgesics (lidocaine) infiltrated in the perineum were the pain killers of the second stage.

If there were insufficient uterine contractions in the 2nd stage of labor, this was corrected using oxytocin infusion to achieve regular uterine contractions; (three or more uterine contractions in 10 minutes each lasting >40 seconds). AVD was done when the 2nd stage of labor was prolonged for more than 2 hours for nullipara patients and more than one hour for multipara patients. Presumed fetal distress was diagnosed by electronic fetal monitoring which has a higher false positive rate for detection of fetal hypoxia and acidosis. Further investigation by fetal blood scalp sampling and PH measurement is usually indicated to avoid unnecessary intervention, but unfortunately our unit does not have a fetal blood PH sampling machine. Maternal exhaustion and fatigue was diagnosed when the mother's pushes were insufficient to descend the presenting part further.

Unsuccessful trial of AVD was elicited with failure of descent of the presenting part after three successive pulls or five pop-offs of the vacuum cup with resort to lower uterine segment caesarian section.

Maternal complications that were reported from the medical records of the patients constituted different degrees of vaginal

**Table 1**

	Prerequisites for operative vaginal delivery
Full abdominal and vaginal delivery	<ul style="list-style-type: none"> <li>• Head is <math>\leq 1/5</math> palpable per abdomen</li> <li>• Vertex presentation</li> <li>• Cervix is fully dilated and membranes ruptured</li> <li>• Exact position of the head can be determined so proper placement of the instrument can be achieved</li> <li>• Pelvis is deemed adequate</li> </ul>
mother	<ul style="list-style-type: none"> <li>• Informed consent is obtained and clear explanation given</li> <li>• Maternal bladder has been emptied recently</li> <li>• Indwelling catheter should be removed or balloon deflated</li> <li>• Aseptic techniques</li> </ul>
staff	<ul style="list-style-type: none"> <li>• Operator must have the knowledge, experience and skills necessary to use the instruments</li> <li>• Adequate facilities and back-up personnel are available</li> <li>• Back-up plan in place in case of failure to deliver anticipation of complications that may arise (e.g. shoulder dystocia, postpartum hemorrhage)</li> <li>• Personnel present who are trained in neonatal resuscitation</li> </ul>

or perineal tears and postpartum hemorrhage. The diagnosis of the postpartum hemorrhage relied on estimation of blood loss >500cc with drop of PCV value  $\geq 5$ . Fetal complications were reported by reviewing the medical records of the babies.

The aim of this study was to determine the rate, indications and short term maternal and neonatal complications of AVD in two military hospitals in the south of Jordan.

## Results

In this study, a total of 8,791 deliveries in the years 2012 to 2015 were performed after excluding preterm deliveries and breech deliveries (976 case). During the study period 238 successful instrumental deliveries were done with a rate of 2.7%. The mean maternal age of the study population was 26.45 years and the mean parity was 1.1 (Table 2). Out of these 238 patients, 136(57.14%) were primigravidas; the remaining were multigravida (parity range 1-8).

**Table 2**

Mode of delivery	No. of patients	Percentage
NVD	7195	73.67%
CS	2332	23.87%
AVD	238	2.7%

The main instrument used was metallic vacuum cup (202/238) and (36/238) deliveries were performed using obstetrics forceps. 20 LUSC/S were undergone after unsuccessful trials of vacuum assisted vaginal deliveries. A zero failure rate was found using the forceps. The commonest indication for AVD was presumed fetal distress (Table 3). The maternal and fetal complications reported are shown in (Table 4) where the commonest maternal complication was different degrees of genital tract tears (25/238) and three of these patients needed repair under general anesthesia. The postpartum hemorrhage which afflicted 18 patients was mainly secondary to genital tract trauma followed by the uterine atony and the majority of these ladies received blood products.

Fetal complications registered consisted of (11) cases of Erbs palsy, (12) cases were admitted to NICU for observation and one case of cerebral palsy (Table 5). The main cause of new born admissions to the neonatal intensive care unit (NICU) was for observation to rule out sepsis due to prolonged premature rupture of membranes. All the admissions were discharged home well except three cases. One was referred to King Hussein Medical Center due to suspected intestinal obstruction, another was diagnosed to have Rh incompatibility, and the third one was diagnosed to have cerebral palsy on follow up visits.

**Table 3**

Number of patients	Parity
136	Primigravida
36	Para 1
27	Para 2
12	Para 3
11	Para 4
16	Para 5 or more

**Table 4**

Number of patients	Indication of AVD
13	Presumed fetal jeopardy
85	Prolonged 2nd stage of labour
12	Maternal fatigue and exhaustion

**Table 5**

Complication		Percentage	Total No.
Maternal	Postpartum hemorrhage	7.56%	18
Maternal	Genital tract injuries	10.5%	25
Fetal	Admission to NICU	8.4%	20
Fetal	Clavicular fracture	1.68%	4
Fetal	Erb's palsy	3.78%	9
Fetal	Subdural hematoma	0.42%	1

## Discussion

Overall instrumental delivery rates worldwide are around 10%, but vary widely from 1.5 of deliveries in Czech Republic to 15% in Canada. Even within a single country, the range is wide (e.g. in Scotland, from 4% to 26% in primiparous women(3), and in the United States 1-23 percent(4).

The precise incidence of operative vaginal delivery in the United States is unknown, but forceps or vacuum delivery was coded over the birth certificate as the method of delivery for 8% of vaginal births in 2002(5). The total rate of operative vaginal delivery in 2014, the last year for which complete data are available in the United States, was only 3.1%. Obstetric forceps were used in 0.57% of deliveries and 2.64% were delivered via the vacuum extractor (6). So in most countries the overall rate is reasonably constant, but there is a gradual move away from forceps towards vacuum due to the perception that vacuum is easier and safer to use.

In our study the incidence of instrumental deliveries was 2.7% which is much below the average rate; this might be attributed to more than one factor.

First, the lack of use of regional anesthesia as routine in the labour rooms. This is now well documented to increase the incidence of instrumental deliveries (7,8) by several mechanisms, one mechanism being the reduction in serum oxytocin level which results in a weakening of uterine activity and this may be due in part to intravenous fluid infusion being given before epidural analgesia. Maternal effort at expulsion can also be impaired, causing fetal malposition during descent (9). Five trials that included 2703 nulliparous women were analyzed by Sharma and colleagues (2004). Women given epidural analgesia had a two fold increase in rate of instrumental delivery compared with those given parenteral analgesia - 13 versus 7% (8).

The second factor participating in the low rate in our set up is the lack of experience of the delivery room attending obstetricians (most of the time they are residents).

Lastly, the fear of potential neonatal complications and possible litigation in courts makes them resort to the abdominal delivery as a reasonable alternative.

Maternal indications of operative vaginal delivery are most commonly due to maternal distress, maternal exhaustion, or undue prolongation of the second stage of labor (2, 12). Fetal indications commonly encountered are malposition of the fetal head, with relative dystocia which occurs more frequently with regional anesthesia (4). Fetal distress is a commonly cited indication. This expression is subject to varied interpretation which may range from a brief bradycardia to prolonged late decelerations with acidosis. So a "presumed fetal jeopardy" may be a preferable term(1), in conjunction with recording of as precise a description of the situation as possible in order to validate the indication. Presumed fetal jeopardy was the main indication of operative vaginal delivery in our study (132/238) 55.46% followed by prolonged second stage of labor (85/238) 35.7%

Most of the complications of AVD have also been reported following spontaneous vaginal and even abdominal deliveries, but their incidence is greater with AVD(1).

Maternal complications are usually those of soft tissue trauma and tend to be reported more frequently with the use of forceps than with ventouse (12); they can include uterine, cervical or vaginal injury, laceration or hematomas and the consequent risk of postpartum hemorrhage. In this study 25 patients had genital tract injuries (perineal, vaginal, and cervical) and 18 cases had postpartum hemorrhage (7.56%), of which 11 were secondary to genital tract trauma, and the remainder were caused by uterine atony.

Data from several sources, including several large randomized trials performed in industrialized countries, indicate that the prevalence rate of PPH of more than 500 mL is approximately 5% when active management is used (which is adopted in our hospitals) versus 13% when expectant management is used(13). Cervical laceration is most commonly associated with forceps delivery, and the cervix should be inspected following all such deliveries. Vaginal sidewall laceration is also most commonly associated with operative vaginal delivery.

Fetal complications of forceps delivery include transient facial marks, facial nerve palsies and fracture of facial bone or skull (1). Injuries from vacuum include minor and occasionally severe scalp injuries, including scalp bruising, abrasions, lacerations, cephalhematoma, subgaleal hematoma and intracranial hemorrhage (12). 9 babies whose deliveries were complicated by shoulder dystocia suffered from Erbs palsy with concomitant clavicular fractures in 4 of them. Shoulder dystocia and its

peripheral nerve palsy complications (Erb's palsy) are slightly more common after AVD than after spontaneous delivery. The risk of shoulder dystocia is now mainly with vacuum use. This may be related to the physics of extraction, specifically the vector of force generated by the vacuum cup versus forceps(10,12,13). Unfortunately we could not elicit the incidence of shoulder dystocia in this study due to the poor notes in the medical records.

The only severe fetal complication reported was for a baby who was an outcome of vacuum delivery with an indication of fetal distress and cord prolapse. This baby was delivered with a low Apgar score at 5 minutes and had bilateral cephalhematoma and was ventilated for three days. His brain CT scan showed subdural hematoma and he was diagnosed to have hypotonic ataxic cerebral palsy on follow up visits. In literature the reported incidence of fetal death or severe fetal injury from vacuum extraction is low, ranging from 0.1-3 cases per 1,000 procedures (10).

## Conclusion

Our study showed a lower rate of operative vaginal delivery in comparison to the international figures. This may be attributed to the lack of epidural anesthesia which increases the incidence of instrumental deliveries, in addition to the simple experience of the attending residents who fear possible complications of applying these instruments and the consequent litigation. The complications reported in our study were expected in assisted vaginal deliveries and mimic those mentioned in the literature.

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# White coat hypertension may be an initial sign of an accelerated atherosclerotic process

Mehmet Rami Helvaci (1)

Orhan Ayyildiz (1)

Orhan Ekrem Muftuoglu (1)

Mustafa Yaprak (2)

Abdulrazak Abyad (3)

Lesley Pocock (4)

(1) Professor of Internal Medicine, MD

(2) Assistant Professor of Internal Medicine, MD

(3) Middle-East Academy for Medicine of Aging, MD, MPH, MBA, AGSF, Chairman

(4) medi+WORLD International, Australia

## Correspondence:

Mehmet Rami Helvaci, M.D.

Alanya, Antalya,

Turkey

Phone: 00-90-506-4708759

Email: mramihelvaci@hotmail.com

## ABSTRACT

**Background:** Role of white coat hypertension (WCH) is unknown in metabolic syndrome.

**Methods:** The study was performed in the Internal Medicine Polyclinic.

**Results:** The study included 1,068 patients (628 females). Prevalence of excess weight increased from the third (28.7%) up to the seventh decades (87.0%), gradually ( $p < 0.05$  nearly in all steps), and then decreased in the eighth decade of life (78.5%,  $p < 0.05$ ). The most significant increase was detected during the passage from the third to the fourth decade (28.7% versus 63.6%,  $p < 0.001$ ) parallel to the smoking. Similarly, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired glucose tolerance (IGT), and WCH increased up to the seventh decade of life and decreased afterwards ( $p < 0.05$  nearly in all steps). On the other hand, hypertension (HT), type 2 diabetes mellitus (DM), and coronary heart disease (CHD) always increased without any decrease by decades ( $p < 0.05$  nearly in all steps) indicating their irreversible properties.

**Conclusion:** Probably metabolic syndrome is an accelerated atherosclerotic process all over the body. It includes some reversible parameters such as smoking, alcohol, sedentary life style, animal-rich diet, overweight, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, IGT, and WCH for the development of terminal illnesses such as early aging, obesity, DM, HT, peripheral artery disease, chronic obstructive pulmonary disease, cirrhosis, CHD, and stroke. The terminal illnesses are mainly due to the chronic inflammatory process on the arterial endothelial systems due to the much higher blood pressure in them. WCH may be an initial sign of the accelerated atherosclerotic process that can be detected easily.

**Key words:** White coat hypertension, metabolic syndrome, atherosclerosis, aging.

## Introduction

Causative relationships between accelerated atherosclerosis and smoking, alcohol intake, sedentary life style, animal-rich diet, and excess weight have been known for many years under the title of metabolic syndrome (1, 2). The syndrome is characterized by a low-grade chronic inflammatory process on endothelial systems, particularly on the arterial endothelial systems, probably due to much higher blood pressure (BP) in them. The inflammatory process may be slowed down with nonpharmaceutical approaches including lifestyle changes, diet, and regular exercise before the development of end-organ insufficiencies (3, 4). Probably the metabolic syndrome includes reversible parameters such as smoking, alcohol, sedentary life style, animal-rich diet, overweight, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and white coat hypertension (WCH) for the development of terminal illnesses such as early aging, obesity, type 2 diabetes mellitus (DM), hypertension (HT), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), cirrhosis, coronary heart disease (CHD), and stroke (5). In another definition, the syndrome induced accelerated atherosclerosis may be the leading cause of death in human beings. On the other hand, WCH is a well-known clinical entity defined as the persistently elevated BP in doctor's office whereas normal at home. It was reported in an Ohasama study that WCH is a risk factor for development of home HT (6). Similarly, intima-media thickness and cross-sectional areas of carotid artery were found similar in patients with WCH and HT, which were significantly higher than the patients with sustained normotension (NT) (7). Additionally, plasma homocysteine levels were higher, and left ventricle mass index was greater in the WCH compared to the sustained NT groups ( $p < 0.001$  for both) (7). We tried to understand the role of WCH in the definition of the metabolic syndrome in the present study.

## Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at and above the age of 20 years were taken into the study. Their medical histories including smoking habit, DM, dyslipidemia, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and an electrocardiography were performed. Current smokers with six pack-months and cases with a history of five pack-years were accepted as smokers, and cigar or pipe smokers were excluded. Alcohol was not included due to the very low prevalence of alcohol use in Kutahya region of Turkey. Patients with devastating illnesses including type 1 DM, malignancies, acute and chronic renal failure, decompensated cirrhosis, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on body weight. Body mass index (BMI) of each patient was calculated by the measurements of the same physician instead of verbal expressions. Body weight in kilograms is divided by height in meters squared, and underweight is defined with a BMI of lower than 18.5, normal weight with 18.5-24.9, overweight with 25-29.9,

and obesity with a BMI of 30.0 kg/m<sup>2</sup> or higher (8). Patients with an overnight FPG level of 126 mg/dL or greater on two occasions were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or higher is DM and between 140-199 mg/dL is IGT. Patients with dyslipidemia were detected by using the National Cholesterol Education Program Expert Panel's recommendations (8). Dyslipidemia is diagnosed when LDL-C is 160 or higher and/or TG is 200 or higher and/or HDL-C is lower than 40 mg/dL. A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or with a history of angina pectoris. Coronary angiography was obtained for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with a history of coronary artery stenting and/or coronary artery bypass graft surgery. Office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after a brief education about proper BP measurement techniques (9). An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained just in cases with higher OBP and/or HBP measurements. It was performed with oscillometrical equipment (SpaceLabs 90207, Redmond, Washington, USA) set to take a reading every 10 minutes throughout the 24-hours. Normal daily activities were allowed, and subjects were told to keep the arm relaxed during measurements. Eventually, HT is defined as a BP of 135/85 mmHg or higher on mean daytime ABP (between 10 AM to 8 PM) (9). WCH is defined as an OBP of 140/90 mmHg or higher, but mean daytime ABP of <135/85 mmHg (9). Eventually, prevalence of smoking, excess weight, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, IGT, WCH, DM, HT, and CHD were detected for the decades and compared in between. Comparison of proportions was used as the method of statistical analysis.

## Results

The study included 1,068 patients (628 females and 440 males). Due to just 20 patients in the ninth decade, they were not included for the statistical comparison. There were only 1.7% (19) of cases with underweight and 28.7% (307) of cases with normal weight, so 69.4% (742) of cases at and above the age of 20 years had excess weight including overweight and obesity. The prevalence of excess weight increased from 28.7% in the third to 87.0% in the seventh decades, gradually ( $p < 0.05$  nearly in all steps), and then decreased to 78.5% in the eighth ( $p < 0.05$ ) and to 60.0% in the ninth decade of life. Interestingly, the prevalence of excess weight showed its most significant increase during the passage from the third to the fourth decades of life (28.7% versus 63.6%,  $p < 0.001$ ). Prevalence of smoking had a significant increase during the passage from the third to the fourth decades of life too (11.0% versus 32.4%,  $p < 0.001$ ). Prevalence of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH had a similar fashion to the excess weight, increasing until the seventh decade of life and decreasing afterwards, significantly ( $p < 0.05$  nearly in all steps). On

the other hand, prevalence of HT, DM, and CHD always increased without any decrease by decades, significantly ( $p < 0.05$  nearly in all steps), indicating their irreversible properties. On the other hand, 517 cases with WCH and HT were diagnosed both via HBP and ABP, and no difference

was observed between the two methods according to the total number of patients diagnosed. Mean systolic/diastolic OBP, HBP, ABP values and mean heart rates of the groups are summarized in Table 2 (next page).

**Table 1: Characteristics of the study cases**

Variables	Third decade	<i>p</i> -value	Fourth decade	<i>p</i> -value	Fifth decade	<i>p</i> -value	Sixth decade	<i>p</i> -value	Seventh decade	<i>p</i> -value	Eighth decade
Number	181		157		246		249		108		107
Prevalence of smoking	11.0%	***	32.4%	ns†	28.8%	ns	31.7%	ns	23.1%	ns	23.3%
Prevalence of excess weight	28.7%	***	63.6%	***	78.4%	ns	83.1%	ns	87.0%	*	78.5%
Prevalence of hyper-betalipoproteinemia	1.6%	***	12.7%	ns	15.8%	ns	19.6%	ns	23.1%	*	14.0%
Prevalence of hyper-triglyceridemia	5.5%	***	15.2%	*	20.3%	*	25.7%	ns	24.0%	**	11.2%
Prevalence of dyslipidemia	6.6%	***	26.7%	ns	31.7%	*	38.9%	ns	39.8%	***	20.5%
Prevalence of IGT‡	0.5%	ns	1.2%	***	10.1%	***	19.6%	ns	21.2%	ns	15.8%
Prevalence of white coat hypertension	23.2%	ns	24.2%	**	33.3%	***	44.5%	ns	40.7%	**	25.2%
Prevalence of diabetes mellitus	0.5%	ns	1.9%	***	11.7%	***	21.6%	ns	25.0%	ns	26.1%
Prevalence of hypertension	0.0%	**	5.0%	***	10.4%	***	20.4%	**	31.4%	ns	38.3%
Prevalence of CHD§	0.0%	ns	0.0%	*	3.6%	***	12.8%	**	22.2%	ns	24.2%

\* $p < 0.05$  \*\* $p < 0.01$  \*\*\* $p < 0.001$  †Nonsignificant ( $p > 0.05$ ) ‡Impaired glucose tolerance §Coronary heart disease

**Table 2: Mean blood pressure values of the study cases**

Variables	Sustained normotension (n=551)	WCH* (n=349)	Hypertension (n=168)
Prevalence	51.5%	32.6%	15.7%
Mean age (year)	38.8 ± 12.3 (15-83)	48.2 ± 11.3 (15-79)	55.3 ± 10.3 (33-85)
Female ratio	57.1% (315)	63.3% (221)	65.4% (110)
Mean OBP†	117.3 ± 4.7/78.3 ± 5.1	153.3 ± 5.4/97.3 ± 9.3	167.5 ± 5.6/108.3 ± 5.7
Mean HBP‡	97.7 ± 13.3/73.1 ± 5.1	121.1 ± 5.5/74.1 ± 5.3	149.5 ± 6.3/97.3 ± 7.3
Mean ABP§	Not performed	123.7 ± 5.3/77.1 ± 5.3	150.7 ± 7.7/98.7 ± 7.3
Mean heart rate (beat/minute)	65.1 ± 11.5 (52-129)	75.3 ± 13.3 (61-149)	80.5 ± 11.3 (63-167)

## Discussion

Probably metabolic syndrome contains a group of reversible parameters for the development of terminal illnesses, those developed due to the accelerated atherosclerotic process all over the body. The accelerated atherosclerosis may be the leading cause of death in human beings. So definition of the syndrome includes reversible parameters such as smoking, alcohol, animal-rich diet, sedentary life style, overweight, WCH, IFG, IGT, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia for the development of terminal diseases such as early aging, obesity, HT, DM, PAD, COPD, cirrhosis, CHD, and stroke (10, 11). Parallel to the excess weight, prevalence of hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, IGT, and WCH increased until the seventh decade of life and decreased afterwards in the present study ( $p < 0.05$  nearly in all steps). On the other hand, prevalence of HT, DM, and CHD always continued to increase without any decrease by decades showing their irreversible properties ( $p < 0.05$  nearly in all steps). Probably after development of one of the terminal diseases, the non-pharmaceutical approaches will provide little benefit to prevent development of the others due to cumulative effects of the risk factors on endothelial systems for a long period of time, especially on the arterial endothelial systems due to the much higher BP in them (10, 11). According to our opinion, obesity should be included among the terminal diseases of the metabolic syndrome since after development of obesity, nonpharmaceutical approaches will provide little benefit either to reverse obesity or to prevent its complications.

WCH is associated with some features of the metabolic syndrome (12), and more than 85% of cases with the syndrome have elevated BP levels (4). We observed high prevalence of WCH even in early decades of life in the present study, for example 23.2% in the third and 24.2% in the fourth decades. The high prevalence of WCH in society was also shown by some other authors in the literature (13-15). When we compared the sustained NT, WCH, and HT groups in another study (16),

prevalence of nearly all of the health problems including IGT, obesity, DM, and CHD had significant progressions from the sustained NT towards the WCH and HT groups, and the WCH group was found as a progression step in between. But as an interesting finding, the prevalence of dyslipidemia was the highest in the WCH group, and it was 41.6% among them whereas they were 19.6% in the sustained NT ( $p < 0.001$ ) and 35.5% in the HT groups ( $p < 0.05$ ) (16). Similar results showing the higher prevalence of dyslipidemia among the WCH cases were also observed in another study (17), whereas serum TG and cholesterol levels did not differ significantly between NT, WCH, and sustained HT cases in men in another study (18). The relatively lower prevalence of dyslipidemia in the HT group may be explained by the already increased adipose tissue per taken fat in them, since prevalence of obesity was significantly higher in the HT against the WCH groups (52.8% versus 44.1%,  $p < 0.01$ ) (16). So the detected high prevalences of WCH even in early decades, despite the low prevalences of excess weight in these age groups, may show a trend of weight gain and its terminal consequences. Probably all of the associations are closely related with the metabolic syndrome since WCH and dyslipidemia may be two initial signs of the syndrome. On the other hand, we accept the WCH as a different entity from borderline/mild HT due to the completely normal HBP and ABP measurements in the WCH, whereas they are abnormal in mild HT cases, but both groups of patients will get benefit from life style changes such as cessation of smoking and alcohol, regular physical activity, and animal-poor diet.

Weight gain and smoking may be the major triggering causes of the metabolic syndrome (19). Although smoking may cause some weight loss, its effect is probably due to the chronic endothelial inflammation all over the body, since loss of appetite is one of the initial symptoms of systemic inflammations. In another definition, smoking induced weight loss is an indicator of disease but not health. Similarly, excess weight leads to a chronic and low-grade inflammatory process on the endothelial systems, particularly on the arterial endothelial systems due to the much higher BP in them, and risk of death from all causes

including cardiovascular diseases and cancers increases parallel to the range of moderate to severe weight excess in all age groups (20). The effects of body weight on BP were also shown previously, that the prevalence of sustained NT was significantly higher in the underweight (80.3%) than the normal weight (64.0%) and overweight groups (31.5%,  $p < 0.05$  for both) (21), and 55.1% of cases with HT had obesity against 26.6% of cases with sustained NT ( $p < 0.001$ ) (22). So the weight gain may be the main triggering factor for insulin resistance, dyslipidemia, IGT, and WCH (4). Stopping of weight gain with animal-poor diet, regular exercise, and cessation of alcohol, even in the absence of a prominent weight loss, will result with resolution of many parameters of the syndrome (23-25). But according to our opinion, limitation of excess weight as an excessive fat tissue in and around abdomen under the heading of abdominal obesity is meaningless, instead it should be defined as overweight or obesity via BMI, since adipocytes function as an endocrine organ that produces a variety of cytokines and hormones anywhere in the body (4). The resulting hyperactivity of sympathetic nervous system and renin-angiotensin-aldosterone system is probably associated with chronic endothelial inflammation, elevated BP, and insulin resistance. Similarly, the Adult Treatment Panel III reported that although some people classified as overweight with a large muscular mass, most of them also have excess body fat, and excess weight does not only predispose to CHD and stroke; it also has a high burden of other CHD risk factors including dyslipidemia, type 2 DM, and HT (8).

As a conclusion, metabolic syndrome may be an accelerated atherosclerotic process all over the body. It includes some reversible parameters such as smoking, alcohol, sedentary life style, animal-rich diet, overweight, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, IFG, IGT, and WCH for the development of terminal illnesses such as early aging, obesity, DM, HT, PAD, COPD, cirrhosis, CHD, and stroke. The terminal illnesses are mainly due to the chronic inflammatory process on the arterial endothelial systems due to the much higher BP in them. WCH may be an initial sign of the accelerated atherosclerotic process that can be detected easily.

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