

Prevalence of Abnormal Cervical Smear at Yashfeen Gynaecological Clinic Tripoli, 2009-2012

Najwa Eljabu^{@1,2} and Abdulhafid Abudher²

¹Department of Gynaecology and Obstetrics, Tripoli University Hospital

²Department of Gynaecology and Obstetrics, Faculty of medicine, University of Tripoli, Libya

Received 12 August 2019/Accepted 1st December 2019

ABSTRACT

Cervical cancer is the third most common cancer in the world, with 2.3 million prevalent cases and 510,000 incident cases documented each year. Pap smear screening identifies abnormal premalignant cells at the cervical transformation zone; this resulted in reduction of cervical cancer incidence and mortality rates by 70% in developed countries. The study conducted to determine the incidence of abnormal Pap smears among gynaecological patients at Yashfeen clinic in Tripoli. A retrospective study included all Pap smears reported between 1st January 2009- 31st December 2012 for Libyan women, at Yashfeen Clinic in Tripoli. All cytological smears were collected by Ayre's spatula and slides were evaluated at Elzawia laboratories by consultant cytologist. A total of 507 cervical cytology specimens were reviewed and classified according to Bethesda system. A total of 507 Pap smear reports were reviewed from patients aged between (19-70) years. 493 (97%) were found satisfactory for analysis, and of these 130 (26%) were normal, while 344 (70%) had benign cellular changes in the form of inflammatory smears. There were 19 (4%) abnormal smears with epithelial cell abnormalities, of which 14 (3%) had atypical squamous cells of undetermined significance (ASCUS), and 5 (1%) had low grade squamous intraepithelial lesions (LSIL). There were no cases of atypical glandular cells of undetermined significance (AGUS) or high grade squamous intraepithelial lesions (HSIL) or squamous cell carcinoma (SCC) among this sample of smears. The prevalence of (LSIL) and (ASCUS) is low in this study. Overall, 4% of routinely screened women were found to have an abnormal cervical smear.

Key words- Pap smear; Screening; Cervical cancer; Neoplasia.

INTRODUCTION

Cervical cancer is the fourth most frequent cancer in women with an estimation of 570,000 new cases in 2018 representing 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries.¹

The major risk factors for cervical cancer are well documented including sexual habits (age of first sexual intercourse and the number of sexual partners), infection with human papilloma virus, low socio-economic status, marrying before age 18 years and cigarette smoking.²

The majority of the screening programs worldwide are using pap smear methods and attempting to imitate the excellent outcome achieved in developed countries, Finland is the best worldwide example for decreasing in cervical cancer incidence as a result of a well organised screening program.³

Pap smear screening identifies abnormal premalignant cells at the cervical transformation zone; this resulted in reduction of cervical cancer incidence and mortality rates by 70% in developed countries.⁴

Cervical screening helped to decrease cervical cancer rate, since Pap smear implementation from 1950s.⁵ A dramatic reduction has been observed in the incidence and mortality of invasive cervical cancer worldwide as a result of introduction of the Pap smear. This is because of the ability of Pap smear to recognise early precancerous changes and the availability of effective treatments.⁶

The International Agency for Research on Cancer (IARC) determined that the incidence of invasive cervical cancer can be reduced by at least 80% with the implementation of cervical cancer screening programs based on Pap test every three to five years for women of ages 35 to 64.⁷

It suggested that five yearly screening of women aged 20 to 65 years could reduce the incidence of invasive cancer by 84%. Three-yearly screening could reduce the incidence by 91% and annual screening could reduce the incidence by 93%.⁸ National Institute of Clinical Excellence (NICE) concluded that liquid based cytology (LBC) represented a cost-effective alternative to Papanicolaou smears, offering improved sensitivity without any reduction in specificity, and a reduction in the number of inadequate tests reported.⁹



Screening with use of Pap smear, liquid based cytology and human papilloma virus with use of DNA testing have contributed significantly to the reduction of cervical cancer in developed countries, and more recently visual inspection with acetic acid (VIA), which is easy, costs effective and fits well to low resource countries.¹⁰

Effective programs must meet targets: at least 70% of the targeted population should be screened at least once in a lifetime; screening assays and diagnostic tests must be reproducible and sufficiently sensitive; and specificity for the detection of high-grade precursor lesions and effective treatment must be provided.¹¹

For counselling young women and for organising a public health system it is important to know the incidence of cervical intraepithelial lesions in a country. Therefore, the aim of this study was to estimate the incidence and pattern of abnormal Pap smears based on Bethesda system among gynaecological patients at Yashfeen Clinic in Tripoli between 1st January 2009- 31st December 2012.

MATERIALS AND METHODS

A retrospective cohort study, aimed to evaluate all Pap smears reported between 1st January 2009- 31st December 2012 was conducted at Yashfeen private gynaecological Clinic, Tripoli, Libya.

All cytological smears were collected by Ayre's spatula and slides were evaluated at the cytology lab in Elzawia laboratories by consultant cytologist. A total of 507 cervical cytology specimens were reviewed and classified according to Bethesda system.

The following cytological diagnoses were used:

- Benign cellular changes: including infection and reactive changes and epithelial cell abnormalities including squamous and glandular cell changes.
- Atypical squamous cells of undetermined significance (ASCUS).
- Atypical glandular cells of undetermined significance (AGUS).
- High- and low-grade intraepithelial lesion (HSIL) and (LSIL).
- Squamous cell carcinoma (SCC).
- When there were no cellular changes: negative Pap smear result was reported.

Statistical analysis of collected data was performed using the SPSS IBM version 20. The results were expressed in frequencies, means, percentages, and tables.

RESULTS

A total of 507 Pap smear reports were reviewed from patients, all were Libyan, 96% were from Tripoli. The age of the cases ranged from 19 to 70 years old with a mean age of 38.8 ± 8.7 years and most of the cases among age group 25-44 years; 13.4 % of patients were menopause. Contraceptive use and hormonal therapy reported among 7.3%, 1.2% of cases, respectively (Table 1).

Table 1: Demographic and reproductive data of 507 cases

Item	Number	Percentage
Age		
25>	22	4.3%
25-44	362	71.4%
45-70	123	24.3%
Parity		
P0-P1	108	21.3%
P2-P3	197	38.9%
P4≤	202	39.8%
Pregnancy		
Yes	6	1.2%
No	501	98.8%
Postnatal		
Yes	10	2%
No	497	89%
Contraceptive use		
Yes	37	7.3%
No	470	92.7%
Menopause		
Yes	68	13.4%
No	439	86.6%
Hormonal therapy		
Yes	6	1.2%
No	501	98.8%
Pelvic infection		
Yes	17	3.4%
No	490	96.6%
Hysterectomy		
Total	16	3.2%
Subtotal	4	0.8%
No	487	96%
Residence		
Tripoli	487	96%
Outside Tripoli	20	4%



Abnormal cervical cytology classified by the Bethesda system, of the 507 Pap smears, 493 (97%) were found satisfactory (adequate smear); adequate smear was assessed according to the presence of endocervical cells. There were 130 (26%) of cases had normal smear, while 344 (70%) had benign cellular changes in the form of inflammatory smears. There were 19 (4%) abnormal smears with epithelial cell abnormalities, of which 14 (3%) had ASCUS, and 5 (1%) had low grade squamous intraepithelial lesions (LSIL). There were no cases of atypical glandular cells of undetermined significance (AGUS) or high grade squamous intraepithelial lesions (HSIL) or squamous cell carcinoma (SCC) among this sample of smears. The overall rate of abnormal Pap smears was (4%).

Table 2: Cytological diagnosis of 493 Pap smear.

Diagnosis	.No	Percentage
Negative	130	26%
Benign cellular changes	344	70%
ASCUS	14	3%
AGUS	0	0%
LSIL	5	1%
HSIL	0	0%
SCC	0	0%
Total	493	100%

Cytology was performed mostly for routine indications in 467 (92.1%) of cases, and for intermenstrual bleeding (IMB), postcoital bleeding (PCB) in 34 (6.7%) of cases and 6 (1.2%) of cases had postmenopausal bleeding (Table 3).

Table 3: Indications of cervical smear

Indication	Number	Percentage
Routine	467	92.1%
IMB and/or PCB	34	6.7%
PMB	6	1.2%
Total	507	100%

Table 4 showed that clinical appearance of cervix was normal in 448 (88.3%), and cervicitis was reported in 43 (8.5%) of smears (Table 4).

Table 4: Clinical appearance of the cervix

Cervix appearance	Number	Percentage
Normal	448	88.3%
Cervicitis	43	8.5%
Polyps	10	2%
Suspicious	6	1.2%
Total	507	100%

DISCUSSION

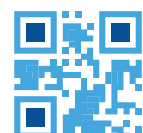
Literature is full with evidences supporting the importance of early detection of premalignant lesions of the cervix by cytological examination using Pap smear. Invasive cancer is preceded by a spectrum of heterogeneous epithelial lesions over a long period. Identification of relevant risk factors and prompt management of the precancerous lesions are important in the prevention of invasive cancer of the uterine cervix. In general, these premalignant lesions are reversible, although the more severe lesions the less the chance of spontaneous regression.¹²

In this study, Pap smear abnormality of 4% is comparable to that reported in other Middle East countries. The rate of abnormal cytology is reported to be 3% in Iranian women¹³, 3.8% in Jordan¹⁴, 4.3% in Kuwait.¹⁵ It is also comparable to some European countries, such as Italy (2.4%)¹⁶, and Belgium (3.7%).¹⁷ However, the rate of cervical cytology abnormalities, in this study, is lower than many countries around the world, such as Russia (9.8%)¹⁸, Romania (5.9%)¹⁹ and India (6.3%).²⁰

The main age of SIL positive women in our study was (40.5 years), which is higher than the western countries. Also, the result of a study in Saudi Arabia showed that, the average age of SIL was lower than our study.²¹ The majority of the SIL diagnoses in our population were the ASCUS category, (Atypical squamous cells of undetermined significance) presenting 14 smears from 19 abnormal smears (73.6%) of SIL cases. Although patients with ASCUS diagnosis are at increased risk for the development of SIL, significance of this diagnosis remains, as its name suggest “Undetermined”. Furthermore, ASCUS diagnosis represents the area of most intra-observer variability among cytologists. Low grade SILs are at substantially increased relative risk of developing high grade SIL and invasive cervical carcinoma compared to the SIL negative population.²² Although most low grade SIL lesions regress completely, the absolute risk of patients with low grade SIL for developing high grade SIL within 2 to 4 years is 10%.²³ Furthermore, HSIL may arise in HPV infected patients without an intervening diagnosis of LSIL. The Bethesda system category of AGUS (Atypical glandular cells of undetermined significance) includes cells of adenocarcinoma in situ as well as cells suspicious for adenocarcinoma of the cervix, which now accounts for (10-20%) of primary cervical cancers.²⁴

In our study, no abnormal Pap smears reported AGUS, this may be explained by that the glandular lesions are often located deep in the endocervical canal and therefore, more difficult to sample with conventional Pap smear tools. Additionally, in conventional Pap smear the cytological features of glandular lesions and carcinoma in situ (CIN) are subtle and often show overlap with the cytological features of CIN. In liquid based cytology, the sensitivity for glandular lesions is increased.²⁵

This together with a better understanding of morphology and aetiology and therefore a higher awareness by pathologists of glandular lesions, could lead to improved recognition of glandular lesions. Additionally, in current



study no SCC (Squamous cell carcinoma) cases are found, this is probably due to small sample size from one private Clinic in eastern Tripoli and therefore community-based studies are required to establish the incidence of SCC.

Our results are comparable with others, that we have relatively lower prevalence of cervical carcinoma and cervical lesions, which is most probably due to sexual behaviours under Islamic rules. In Libya, according to Islamic rules, sexual activity typically begins only after marriage, where the main marital age is over 20 years, and the cultural and religious traditions of our conservative society limit the likelihood of multiple sexual partners. Furthermore, other practices such as male circumcision, which is well established in our country, may play an important role as well. Another probable explanation is that fewer women are screened due to their social and cultural background, and their lack of awareness of the importance of an annual Pap smear.

The limitation to present study should be acknowledged as all retrospective study procedures, such as selection bias. It must also be kept in mind that this hospital-based collection of data and there could be an inherent bias. For a better estimation of the prevalence of cervical disease on larger population-based surveys should be conducted. Visual inspection aided by application of acetic acid is an alternative to cytology screening, yet recent techniques such as HPV DNA testing can be used to identify cervical lesions without reliance on cytology.

The Pap smear limitations also include failure to acquire adequate specimens, inter-observer bias and misinterpretation. Inflammation, scant cellularity and blood contaminating samples have all been considered as causes for inadequate or unsatisfactory samples. On the other hand, HPV testing has a sensitivity of 96% and it decreased the number of colposcopies by 50%. Therefore, combining cytology with HR-HPV testing allows for extended screening intervals if both tests are negative, given its high negative predictive value.²⁶

CONCLUSION

The prevalence of low-grade squamous intraepithelial lesions (LSIL) and atypical squamous cells of undetermined significance (ASCUS) is low in this study, when compared with studies from western world. Overall, 4% of routinely screened women were found to have an abnormal cervical smear.

RECOMMENDATIONS

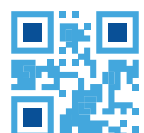
1. Identifying and reaching out to unscreened and under-screened women is our ethical responsibility.
2. Overcoming healthcare barriers and making testing cheaper.
3. Well-designed information campaign should be implemented in national screening programme.
4. Support the preventive efforts through widespread HPV vaccination.

REFERENCES

1. World Health Organization (2019) Cervical cancer, Geneva: WHO. 2019. Available from: <https://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/>.
2. Kashyap N, Krishnan N, Kaur S and Ghai S. (2019) Risk Factors of Cervical Cancer: A case-control study, *Asia Pac J Oncol Nurs.* **6**(3), 308-314.
3. Ibrahim A, Aro AR, Rasch V and Pukkala E. (2012) Cervical cancer screening in primary health care setting in Sudan: a comparative study of visual inspection with acetic acid and Pap smear, *Int J Women's Health* **4**, 67-73.
4. Sait K, Bentley J, Anfinan N and Power P. (2012) Cervical Cancer Prevention in Saudi Arabia: It is Time to Call for Action, *The Open Women's Health Journal* **6**, 1-5
5. Eugenio F, Francesco P, Emanuela M, Alessandro C and Goran G. (2008) History of colposcopy: A brief biography of Hinselmann, *J Prenat Med.* **2**(2), 19-23.
6. Singh S, Nnadi DC, Anas RF, Ango IG, Umar AG, Mohammed U, et al. (2018) Cervical cytology: A review of 597 cases in a tertiary Health Centre in Nigeria, *Case Reports in Clinical Medicine* **7**, 259-268.
7. Chrysostomou AC, Stylianou DC, Constantinidou A and Kostrikis LG. (2018) Cervical cancer screening programs in Europe: The transition towards HPV vaccination and population-based HPV testing, *Viruses* **10**(12), 729.
8. Hong Kong College of Obstetricians and Gynaecologists (2016) Guidelines for cervical cancer prevention and screening. No.4. 2016. Available at: http://www.hkco.org.hk/hkco/Download/Cervical_Cancer_Prevention_and_Screening_revised_November_2016.pdf
9. NHS (2016) Cervical cancer screening program: colposcopy and programme management. 3rd edition. PHE: London, pp.19
10. Sarian LO, Derchain SF, Naud P, et al. (2005) Evaluation of visual inspection with acetic acid (VIA), Lugol's iodine (VILI), cervical cancer cytology and HPV testing screening tools in Latin America, *J Med Screen* **12**(3), 142-149.
11. Gravitt PE, Belinson JL, Salmeron J and Shah KV. (2011) Looking ahead: a case for human papillomavirus testing of self-sampled vaginal specimens as a cervical cancer screening strategy, *Int J Cancer* **129**(3), 517-527.
12. Brink AATP, Zielinski GD, Steenbergen RDM, Snijders PJF and Meijer CJLM (2005) Clinical relevance of human papillomavirus testing in cytopathology, *Cytopathology* **16**, 7-12.
13. Farzaneh F, Jamdar F, Younesi S, Taheri Amin M, Saadati P, Navidpour F, et al. (2019) The trend of abnormal cervical cytology among Iranian women during recent years from 2013 to 2016, *J Obstet Gynecol Cancer Res.* **4**(1), 29-35.
14. Maraqa B, Lataifeh I, Otay L, Badran O, Nouri YQ, Issam I, et al. (2017) Prevalence of Abnormal Pap Smears: A Descriptive Study from a Cancer Center in a Low-Prevalence Community, *Asian Pacific Journal of Cancer Prevention* **18**(11), 3117.
15. Kapila K, George SS, Al-Shaheen A, Al-Ottibi M, Pathan SK, Sheikh ZA, et al. (2006) Changing spectrum of squamous cell abnormalities observed on Papanicolaou smears in Mubarak Al-Kabeer Hospital, Kuwait, over a 13-year period, *Medical Principles and Practice* **15**(4), 253-259.
16. Rossi PG, Ricciardi A, Cohet C, Palazzo F, Furnari G, Valle S, et al. (2009) Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy, *BMC Public Health* **9**(1), 71.
17. Arbyn M, Van Nieuwenhuysse A, Bogers J, De Jonge E, De



- Beeck LO, Matheï C, et al. (2011) Cytological screening for cervical cancer in the province of Limburg, Belgium, *European Journal of Cancer Prevention* **20**(1), 18-24.
18. Shipitsyna E, Zolotoverkhaya E, Kuevda D, Nasonova V, Romanyuk T, Khachatryan A, et al. (2011) Prevalence of high-risk human papillomavirus types and cervical squamous intraepithelial lesions in women over 30 years of age in St. Petersburg, Russia, *Cancer epidemiology* **35**(2), 160-164.
19. Stolnicu S, Musca S, Micu D, Micu L, Moldovan C and Puscasiu L. (2014) Prevalence of abnormal Pap smears in a consecutive and previously unscreened population in Romania, *International Journal of Gynecology and Obstetrics* **124**(2), 156-159.
20. Jena A, Bharathi T, Reddy S, Manilal B, Patnayak R and Phaneendra B. (2012) Papanicolaou (Pap) test screening of staff members of a tertiary care Teaching Hospital in South India, *J Clin Sci Res.* **1**, 174-177.
21. Abdullah LS. (2007) Pattern of abnormal Pap smears in developing countries: a report from a large referral Hospital in Saudi Arabia using the revised 2001 Bethesda System, *Ann Saudi Med.* **27**(4), 268-72.
22. Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J and Robles S. (2005) A critical assessment of screening methods for cervical neoplasia, *International Journal of Gynecology and Obstetrics* **89**(2), S4-S12.
23. Scheungraber C, Kleekamp N and Schneider A. (2004) Management of low-grade squamous intraepithelial lesions of the uterine cervix, *Br J Cancer* **90**(5), 975-978.
24. Adegoke O., Kulasingam S., and Virnig B. (2012) Cervical cancer trends in the United States: a 35-year population-based analysis, *J. Womens Health* **21**, 1031-1037.
25. Bansal B., Gupta P., Gupta N., Rajwanshi A. and Suri V. (2016) Detecting uterine glandular lesions: role of cervical cytology, *CytoJournal* **13**, 3.
26. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. (2010) Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial, *Lancet Oncol.* **11**, 249-257.



Prognostic Value of Doppler Ultrasound in Pre-eclampsia at Tripoli University Hospital (2007-2009)

Hiyam Ben Rajab^{1,2}, Fuad Ali Zekri^{1,2} and Nadia Algantri^{1,2}

¹Department of Gynecology and Obstetrics , Tripoli Medical Center, Libya

²Department of Gynecology and Obstetrics, Faculty of Medicine, University of Tripoli

Received 4 August 2019/Accepted 18 December 2019

ABSTRACT

Doppler ultrasound provides a non-invasive method for the study of fetal hemodynamic. Investigation of the uterine and umbilical arteries gives information on the perfusion of the uteroplacental and fetoplacental circulations. The study aimed to investigate the prognostic value of Doppler ultrasound in assessment of fetal wellbeing in pre-eclamptic pregnant women, and to study the correlation between pulsatility index of umbilical artery, middle cerebral artery, and perinatal outcome in pregnancy with pre-eclampsia. This was a prospective observational study; conducted in Obstetrics and Gynecology Department at Tripoli University Hospital, which includes pregnant women with pre-eclampsia with or without intrauterine growth restriction (IUGR) from January 2007 to December 2009. Variables include umbilical and middle cerebral artery pulsatility index (for fetal outcome), uric acid level, a gestational age at delivery, time interval between last Doppler examination and delivery, Apgar score, and birth weight. A total of 402 patients completed the study, the age ranged from 20-45 years old. The perinatal mortality rate was 6.5%, increased with increase serum uric acid level, and most of babies were preterm (32-34 weeks of gestation) with high perinatal death. The majority of umbilical artery pulsatility index (UMAPI) within normal centile (5th- 95th) with perinatal death of 6%; while the perinatal death of 7.2% were associated with abnormal UMAPI centile, in abnormal middle cerebral artery pulsatility index (MCAPI) centile (<5th) with the perinatal death were 52.2%, among normal MCAPI centile (5th->95th) the perinatal death was 3.7%. The perinatal death increased with birth weight centile <5th centile to 20%, and babies low Apgar score at 5 minutes of delivery with high perinatal death of 68.4%. This study indicates that the Doppler ultrasound is a noninvasive method for study of fetal hemodynamics to give information on the perfusion of the fetoplacental circulation. MCAPI is more sensitive for the perinatal outcome.

Keywords- Doppler ultrasound; Pregnancy; Pre-eclampsia.

INTRODUCTION

Doppler ultrasound provides a non-invasive method for the study of fetal hemodynamic investigation of the uterine and umbilical arteries, gives information on the perfusion of the uteroplacental and fetoplacental circulations.¹ Pre-eclampsia (P.E) and intrauterine growth restriction (IUGR) are associated with an inadequate quality and quantity of the maternal vascular response to placentation, in both conditions, there are characteristic pathological findings in the placental bed.²

Reduced umbilical venous flow volume or increased placental blood flow resistance are the earliest signs of reduced villous perfusion. Absent or even reversal of umbilical artery end diastolic velocity indicates that 60-70% of placental villous vasculature has been damaged with the risk of fetal hypoxemia and potentially acidemia. The late Doppler changes are indicative of advancing circulatory decompensation and potentially impending fetal demise.

The pulsatility index of umbilical artery offers a valuable monitoring measurement even in the absence or reversal of end diastolic velocity.³

The middle cerebral artery (MCA) to umbilical artery (UMA) ratio provides a quick assessment of blood flow without nomograms, the resistance of the cerebral circulation should always be higher than the umbilical resistance (ratio >1). Ratios less than 1 signify brain sparing.⁴

A high correlation with the outcome parameters was found. In the presence of normal flow velocity waves (FVWs), it is sufficient to measure only two arteries, one peripheral and one central. However, the measurement of two additional arteries is of advantage in the event of pathological findings.⁵ The umbilical artery represents the fetoplacental system, and primarily reflects placental resistance.⁶ Growth-retarded fetus with absent or reverse end-diastolic flow in the umbilical artery not only have an increased fetal and neonatal mortality but also a higher incidence of long-term permanent



neurologic damage when compared with growth-retarded fetuses with diastolic flow in the umbilical circulation.⁷ In clinical practice, abnormal end-diastolic umbilical venous pulsation⁷ seems to be a late and ominous sign of a severely compromised fetus. The umbilical artery Doppler indices are usually obtained serially when a fetus is deemed to be at increased perinatal risk.⁸

The current study conducted to study the prognostic value of Doppler ultrasound in assessment of fetal wellbeing in pre-eclamptic patients and to study the correlation between umbilical artery, middle cerebral artery pulsatility index and perinatal outcome in patients with pre-eclampsia.

MATERIALS AND METHODS

This was a prospective observational study conducted in Obstetrics and Gynecology Department at University Hospital, Tripoli, Libya; which includes pregnant women with pre-eclampsia with or without IUGR, from January 2007 to December 2009. Inclusion criteria including viable singleton pregnancy, the gestational age was between 32-38 weeks complicated with pre-eclampsia. Pre-eclampsia was diagnosed according the criteria of the International Society for the study of hypertension in pregnancy. A previous normotensive woman after the 20th week with: diastolic BP ≥ 90 mm Hg measured twice or more ≥ 4 hours apart or diastolic BP ≥ 110 mmHg on any one occasion of pregnancy with proteinuria of ≥ 300 mg/L in 24-hour urine or two clean-catch-midstream or catheter specimens of urine collected ≥ 4 hours apart with $\geq 2+$ on reagent strip. Variables include umbilical and middle cerebral artery pulsatility index (for fetal outcome), uric acid level, a gestational age at delivery, time interval between last Doppler examination and delivery, Apgar score, and birth weight. Umbilical artery velocimetry study was performed at least once a week by means of pulsed Doppler equipment with a 3.5 MHz transducer. Only the results of the last Doppler which was performed within 3 days of delivery were considered in the correlation with perinatal outcomes. An abnormal Doppler velocimetry was defined as pulsatility index being higher than 95th percentile for gestational age, or absent or reversed end diastolic velocity waveforms in umbilical artery, and the pulsatility index in the fetal middle cerebral artery is less than 5th percentile for gestational age, each vessel was measured twice. The difference between the values was always below 6%. The first value was used in most cases, the umbilical artery was examined in any favorable position, the angle between the Doppler beam and the selected vessel was always kept below 60°. The woman was placed in a semi-recumbent position and the transducer was moved to the base of the fetal head, in order to obtain the MCA waveform. Using color flow imaging, the MCA could be seen as a major lateral branch in the circle of Willis, running anterolaterally towards the lateral edge of the orbit. The pulse Doppler sample gate was placed on the proximal portion of this vessel to obtain flow velocity waveforms, Umbilical Artery Doppler waveforms were obtained from the fetal end of the cord, as they are significantly higher than those at the

placental end. The convex transducer was applied to the maternal abdomen with minimal pressure, in order to avoid the effect of fetal head on the cerebral flow impedance. Measurements were performed in the absence of gross fetal body or breathing movements, and at similar heart rate in all groups. Indications for delivery were fetal (non-re assuring non stress test or biophysical profile ≤ 4), or maternal (like headache, blurred vision, epigastric pain, signs of severe pre-eclampsia). Average gestational age at delivery, time interval between the last Doppler examination and delivery, birth weight, Apgar score at 0 and 5 minutes after birth were recorded. Neonatal morbidity will be established if Apgar score < 6 at 5 minutes and neonatal acidemia of pH <7.2 . Birth weight and maturity were estimated by the 1991 US national population; preterm birth was defined as gestational age of <37 completed weeks. Low birth weight was defined birth weight of <2500 g, by using the tables of Alexander and his associates 1996.⁹

Data was analyzed using SPSS program version 16. Descriptive statistics including means, standard deviation, frequencies, and percentages were obtained for all variables as appropriate. *P* value < 0.05 considered significant.

Verbal informed consent was obtained from all participants during their follow up at clinic and data confidentiality was maintained throughout the study and any resulting publication anonymously.

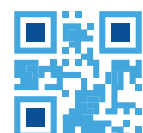
RESULTS

A total 402 patients were included in this study, their age ranged from 20-45 years old with mean age of 30.20 ± 0.22 years. It was found that the perinatal death frequency was 6.5%, 18 babies in the gestational age between 32-34 weeks, and 8 babies in the group of gestational age between 34-36 weeks, and all the babies with their mothers in term pregnancy 37-38 weeks (Table 1).

Table 1: Distribution of cases according to gestational age and perinatal outcomes

Gestational age	With mother	Perinatal death	Total
32-34	214 (92.2%)	18 (7.8%)	232(100%)
35-36	126(94%)	8(6%)	134(100%)
37-38	36 (100%)	0 (0%)	36(100%)
Total	376 (93.5%)	26(6.5%)	402(100%)

Patients were divided into three groups according to their serum uric acid level; there were 164 patients with uric acid level <5 mg/dl with perinatal mortality rate 2.4% , 216 patients with perinatal mortality rate 7.4% among group with uric acid level between 5-7 mg/dl. High uric acid level >7 mg/dl was reported in 22 patients with perinatal mortality rate 27.2% (Figure 1).



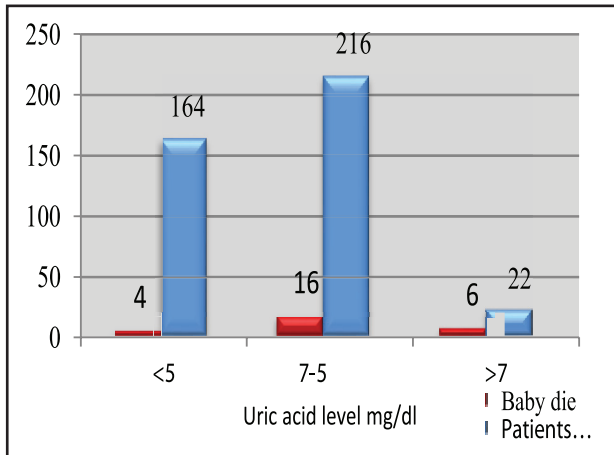


Figure 1: Distribution of perinatal outcomes according to uric acid level

The majority of UMAPI centile between 5th and 95th centile, 204 babies with perinatal mortality rate 6% (n = 12 babies), and 195 babies with umbilical artery PI centile >95th centile had perinatal death 7.2% (Table 2).

Table 2: Distribution of UMAPI centile and perinatal outcome

Centile	With mother	Perinatal death	Total
<5 th	3(100%)	0(0%)	3(100%)
5 th - 95 th	192 (94%)	12(6%)	204(100%)
>95 th	181(92.8%)	14(7.2%)	195(100%)
Total	376 (93.5%)	26(6.5%)	402(100%)

The study showed that, 23 babies with MCAPI<5th centile had very high rate of death (52.2%) and 379 babies were MCAPI between 5th - >95th centile with low mortality rate (3.7%) (Table 3).

Table 3: Distribution of MCAPI centile and perinatal outcome

Centile	With mother	Perinatal death	Total
<5 th	11 (47.8%)	12(52.2%)	23(100%)
5 th - >95 th	365 (96.3%)	14(3.7%)	379(100%)
Total	376 (93.5%)	26(6.5%)	402(100%)

The majority (385) of babies birth weight in this study was found to be between 5th- 95th centile, with mortality rate of 5.9% (n = 23 babies), and 15 babies were <5th centile (low birth weight according to gestational age) with mortality rate 20% and two babies >95th centile and both babies with their mothers (Table 4).

Table 4: Distribution of birth weight centile and perinatal outcome

Centile	With mother	Perinatal death	Total
<5 th	12(80%)	3 (20%)	15(100%)
5 th - 10 th	56(95%)	3(5%)	59(100%)
<10 th -50 th	257(93%)	19(7%)	276(100%)
>50 th -90 th	49(98%)	1(2%)	50(100%)
>90 th -95 th	0 (0%)	0(0%)	0(0%)
>95 th	2(100%)	0(0%)	2(100%)
Total	376 (93.5%)	26(6.5%)	402(100%)

High mortality rate with a low Apgar score at 5 minutes of delivery was found 68.4% (Table 5).

Table 5: Distribution of Apgar score at 5 minute of delivery and perinatal outcome

Apgar score	With mother	Perinatal death	Total
5	6(31.6%)	13(68.4%)	19(100%)
6	5(38.5%)	8(61.5%)	13(100%)
7	8(89%)	1(11%)	9(100%)
8	76(97.4%)	2(2.6%)	78(100%)
9	181(99%)	2(1%)	183(100%)
10	100(100%)	0(0%)	100(100%)
Total	376 (93.5%)	26(6.5%)	402(100%)

DISCUSSION

Fetal arterial Doppler studies are useful in the differential diagnosis of small-for gestation fetuses. In the hypoxic group, due to impaired placental perfusion, the UMAPI is increased and the fetal MCAPI is decreased; consequently, the ratio of PI between the umbilical artery and middle cerebral artery is increased.¹⁰⁻¹³In the current study, most of patients were between 20-45 years old, with mean age of 30 years. In accordance with Meler et al study, which reported the mean age was 31.5 years.¹⁴ More perinatal death with preeclampsia at 32-34 weeks, with no perinatal death at 37-38 weeks were noticed among our patients; which going with Norwegian study at 2015 they found a remarkably high relative risk of fetal death among pregnancies diagnosed with pre-eclampsia in the preterm period. ¹⁵The use of Doppler umbilical waveforms as a fetal surveillance test had gained a wide popularity, especially in high-risk cases.¹⁶ Regarding uric acid level we found 22 patients in our study with high uric acid level more than 7 mg/dl, have high perinatal mortality more than 27%. This finding was similar to results of the study in India, which showed there is a positive correlation between uric acid level and the severity of pre-eclampsia,



and a significant adverse fetal outcome is observed with raised maternal serum uric acid in pre eclamptic patients.¹⁷ In this study an UMAPI when more than 95th centile was with higher perinatal mortality than when it less than 95th centile supported by Romero Arauz et al in Spanish study 2008 which show an abnormal Doppler umbilical artery waveform is associated with poor perinatal outcome and it is a strong predictor of perinatal mortality.¹⁸ In present study, there was less perinatal mortality with birth weight between 5th-95th centile and no fetal death when birth weight more than 95th centile; which simultaneously with different in UMAPI and high mortality rate with low Apgar score at 5 minutes. This also supported by Romero Arauz et al, that showed neonates with abnormal pulsatility index had a lower birth weight (1,174 vs 1,728 g), lower Apgar score at 5 minutes, higher admission to the neonatal intensive care unit (86.4 vs 43%), and significant neonatal morbidity compared with those with normal velocimetry ($P < 0.05$). There were no perinatal deaths with normal umbilical Doppler waveform.¹⁸

Perinatal mortality significantly increase with MCAPI less than 5th centile was noted. This finding is consistent with study done in Turkey; both abnormal umbilical Doppler indices and cerebral-umbilical ratio are strong predictors of IUGR and of adverse perinatal outcome in preeclampsia, the combination of umbilical and fetal cerebral Doppler indices may increase the utility of Doppler ultrasound in pre eclamptic patients.¹⁹

CONCLUSION

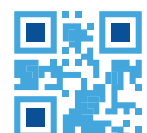
The study concludes that Doppler ultrasound provides a non-invasive method for the study of fetal hemodynamic investigation of the umbilical and middle cerebral arteries; gives information on the perfusion of the fetoplacental circulation and perinatal outcome. MCAPI is more sensitive for the perinatal outcome.

RECOMMENDATIONS

Further prospective studies should be undertaken that also include the Doppler evaluation of venous vessels.

REFERENCES

- Nicolaides KH and Sebire NJ. (2015) Management of the red cell isoimmunized pregnancies. In: Kurjak A, Chervenak FA. Text book of perinatal medicine. 3rded. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd.p.959
- Surico D, Bordino V, Cantaluppi V, Mary D, Gentili S, Oldani A, et al. (2019) Preeclampsia and intrauterine growth restriction: Role of human umbilical cord mesenchymal stem cells-trophoblast cross-talk, *PLoSOne* 14(6), e0218437.
- Han VKM, Seferovic MD, Albion CD and Gupta MB. (2012) Intrauterine growth restriction: Intervention strategies. In: Buonocore G, Bracci R., Weindling M [Eds.]. Neonatology: A Practical approach to Neonatal Diseases. Milano, Italy: Springer-Verlag Italia. p. 90.
- Magriples U. (2018) Intrauterine growth restriction. In: Copel JA, D'Alton ME, Feltovich H, Gratacós E, Krakow D, Odibo AO, et al [eds.]. *Obstetric imaging: fetal diagnosis and care*. 2nd ed. Philadelphia: Elsevier inc.p.470-472.
- Meyberg GC, Solomayer EF, Grischke EM and Bastert G. (1999) Does the measurement of four fetal arteries provide more than the measurement of just two arteries in prenatal Doppler sonography?. *Ultrasound ObstetGynecol.* 13, 407-414.
- Krishna U and Bhalerao S. (2011) Placental insufficiency and fetal growth restriction, *JObstetGynecolo India* 61(5), 505-511.
- Valcamonico A1, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, et al. (1994) Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage, *Am J Obstet Gynecol.* 170(3), 796-801.
- Gudmundsson S, Tulzer G, Huhta JC and Marsal K. (1996) Venous Doppler in the fetus with absent end-diastolic flow in the umbilical artery, *Ultrasound ObstetGynecol.* 7, 262-267.
- Sharma D, Shastri S and Sharma P. (2016) Intrauterine growth restriction: Antenatal and postnatal aspects, *Clin Med Insights Pediatr.* 10, 67-83.
- Arduini D and Rizzo G. (1992) Prediction of fetal outcome in small for gestational age fetuses: comparison of Doppler measurements obtained from different fetal vessels, *J Perinat Med.* 20, 29-38.
- Hecher K, Spernal R, Stettner H and Szalay S. (1992) Potential for diagnosing imminent risk to appropriate and small for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow, *Ultrasound ObstetGynecol.* 2, 266-271.
- Gramellini D, Folli MC, Raboni S, Vadora E and Meriardi A. (1992) Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome, *ObstetGynecol.* 74, 416 - 420.
- Arias F. (1994) Accuracy of the middle-cerebral-to-umbilical-artery resistance index ratios in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications, *Am J ObstetGynecol.* 171, 1541-1545.
- Meler E, Figueras F, Mula R, Crispi F, Benassar M and Gómez O. (2010) Gratacós. Prognostic role of uterine artery Doppler in patients with preeclampsia, *Fetal DiagnTher.* 27, 8-13.
- Harmon QE, Huang L, Umbach DM., Klungsoyr K., Engel SM., Magnus P. et al. (2015) Risk of fetal death with preeclampsia, *Obstet Gynecol.* 125(3), 628-635.
- Alfirevic Z and Neilson JP. (1995) Doppler ultrasonography in high-risk pregnancies: systematic review with meta-analysis, *Am J ObstetGynecol.* 172, 1379-1387.
- Nair A, and Savitha C. (2017) Estimation of serum uric acid as an indicator of severity of preeclampsia and perinatal outcome, *Journal of Obstetrics and Gynecology of India* 67(2), 109-118.
- Romero Arauz JF, Ramos León JC, Rivera Velásquez P, Álvarez Jiménez G and Molina Pérez CJ. (2008) Umbilical artery Doppler velocimetry and adverse perinatal outcome in severe pre-eclampsia, *GinecolObstetMex.* 76(8), 440-449.
- Ozeren M, Dinç H, Ekmen U, Senekayli C and Aydemir V. (1999) Umbilical and middle cerebral artery Doppler indices in patients with preeclampsia, *Eur J ObstetGynecolReprodBiol.* 82(1), 11-16.



Knowledge and Attitude Towards Hepatitis B among Pregnant Women Attending Antenatal Clinics at Tripoli University Hospital, 2016-2017

Fatma Elhawil^{1,2}, Nejima Masoud^{1,2} and Gamal Eddin Shakshouki³

¹Gastroenterology and Hepatology Unit, Department of Medicine, Tripoli University Hospital

²Department of Medicine, Faculty of Medicine, University of Tripoli

³National Center of Disease Control, Tripoli, Libya

Received 1st July 2019/Accepted 19 December 2019

ABSTRACT

Hepatitis B virus (HBV) infection is one of the major public health problems in the world. Libya is, considered an area of intermediate endemicity for hepatitis B with mother to child HBV transmission remains an important mode of transmission. Awareness of pregnant women about hepatitis B and the knowledge that it can be prevented through vaccination is important for the effective control of the disease. Hence, the study conducted to assess knowledge and attitude of pregnant women attending antenatal clinic (ANC) in the Tripoli Medical Centre. This was a cross-sectional study conducted at ANC in Tripoli Medical Center, Libya, between 21st December 2016 and 13th April 2017, including 342 pregnant women attending ANC at Tripoli University Hospital. Knowledge and attitude (KA) regarding HBV were assessed using a standardized structured questionnaire. Data was entered and analyzed by excel program using frequencies and percentages.

A total of 342 pregnant women were enrolled in the study. The mean age was 31.2±6.4 years and the majority of the women was from Tripoli. Only (46.8%) of pregnant women had demonstrated an adequate knowledge towards HBV, and 86.3% of the pregnant women had positive attitude regarding HBV.

The study indicates a poor level of knowledge among pregnant women with regards to several aspects of HBV. Hence, there arises a need for policy guidelines along with extensive health education campaigns to manage all aspects of KA of pregnant women regarding HBV.

Key words- HBV; Knowledge; Attitude; Pregnant; Prevention; Libya.

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the major public health problems in the world. It is estimated that worldwide, 2 billion people have evidence of past or present infection with HBV, and 248 million are chronic carriers of HBV surface antigen (HBsAg), particularly in lower middle-income countries (LMICs)¹; they are at risk in developing liver diseases like cirrhosis and hepatocellular carcinoma (HCC). Worldwide, it is estimated that around 686 000 people die each year from the complications of CHB.² Overall, HBV accounts for around 45% of cases of HCC and 30% of cirrhosis, with much higher proportions LMICs.^{1,3} Chronic infection is much more likely to develop in patients infected as infants (90%) and young children (30%).^{4,5} In Africa, the Middle East, and Asia, chronic hepatitis B generally acquired at birth or early in life, has a prevalence that ranges from 2% to 20%, and is among the leading causes of death in those regions. The seroprevalence of HBsAg among general population in Libya was found to be 2.2%. Libya is, therefore, considered an area of

intermediate endemicity for hepatitis B infection.⁵ About 80-90% of infants, who are infected during their first birthday develop chronic infections.⁶ The main modes of transmission of the hepatitis B virus are through exposure to body fluids like blood, semen or vaginal discharge. Sexual contact, sharing contaminated needles, razors, shared tooth brushes and exposure through non-intact skin or mucous membranes can also transmit HBV.⁷⁻⁹

The infectivity of HBV is hundred times higher than the HIV virus⁷. HBV is rarely congenitally acquired, less than 3% of all mother-to-newborn infections; but it is mostly acquired during delivery.^{6,8,10,11}

At least 50% of all HBV infections are asymptomatic, it is often found during routine prenatal screening. Maternal hepatitis B infection during pregnancy does not increase maternal morbidity and mortality, however, it increases the risk of prenatal transmission.¹² Prevention of mother to child transmission (MTCT) is an essential step in reducing the global burden of chronic HBV. Currently recommended



practice to reduce mother-to-child perinatal transmission or horizontal transmission relies on the administration of HBV vaccine which can prevent 70%-95% of HBV infections in infants born to HBeAg and HBsAg-positive mothers⁹ and, in some countries, concurrent administration of hepatitis B immune globulin (HBIG). Vaccination is the most effective method in preventing HBV infection and thus, decreasing the incidence, prevalence of childhood HBV infection and hepatocellular carcinoma in a number of endemic areas.¹⁵⁻¹⁷

Awareness to pregnant women about hepatitis B and the knowledge that it can be prevented through vaccination is important for the effective control of the disease.

KA studies play an imperative role in determining the ambiguities of the society and are widely used in population reported assessment research worldwide. In Libya the current knowledge and attitude (KA) among key affected populations such as pregnant women are unknown. Thus, there is a need for KA study in the country among ANC women towards HBV to better strengthen and improve public health awareness and other intervention on HBV at the health facility setting. Therefore, this study was conducted to assess knowledge and attitude of pregnant women attending Antenatal Clinic (ANC) in Tripoli Medical Centre in Libya as evidence for effective HBV awareness raising and advocacy program.

MATERIALS AND METHODS

A cross-sectional descriptive study design of KA of pregnant women attending ANC in Tripoli Medical Centre, in Libya was conducted for the duration of 4 months from 21st December 2016 to the 13th April 2017. A random sample of pregnant women who agree to participated in the study and give verbal consent were enrolled. A sample size was estimated to be 342 women, a margin of error of 5% (at 95% confidence level), assumed that 50% of respondents were knowledgeable and aware of hepatitis B. A non-response rate of 5% was factored in the sample size calculation.

A structured questionnaire was used, all the questions were closed-ended. The questionnaire explored the socio-demographic background of respondents which include: age, educational level, occupation, residential address. Also, there were questions regarding HBV knowledge and attitude.

The questionnaire consisted of 12 items that assessed participants' knowledge and 4 items for attitude related to HBV. These questions were then scored; each correct response was scored one (1) point (favorable response) and each wrong or "don't know" response was scored zero (0) (unfavorable response).

The total score of the participants' knowledge regarding HBV is 12 (100%), and for positive attitude was 4. The knowledge and attitude level were categorized as "low" for scores within 0-49%, "moderate" for scores within 50-75% and "high" for scores >75%. Unfavourable score was indicated poor knowledge and attitude, and favourable for moderate and high score.

Data was entered and analyzed by SPSS program, version 16. Frequencies and percentages were calculated. A Chi-

square test was conducted to determine the relationship between the categorical variables and the main outcomes of the study (knowledge, attitude related to HBV infection). The P-value of $\leq .05$ was set as the significance level.

RESULTS

A total of 342 women were surveyed. The age ranged between 16-53 years; the main age was 31.2±6.4 years. Most of the cases (272, 79.5%) were among age group 25-44 years. The majority of the participants (293, 85.7%) had secondary degree or above, and (89.5%) of the study participants from Tripoli (Table 1).

Table 1: Socio-demographic data of pregnant women

Character	No.	%
Age (year)		
<25	53	15.5
25-34	168	49.1
35-44	104	30.4
45-54	4	1.2
Unknown	13	3.8
Education level		
Illiterate	14	4.1
Essential	33	9.6
Secondary	159	46.5
College or above	134	39.2
Unknown	2	0.6
Occupation		
Employment	140	40.9
House wife	166	48.5
Student	34	9.9
Unknown	2	0.6
Residence		
Tripoli	306	89.5
Outside Tripoli	36	10.5

Regarding the knowledge toward HBV among the pregnant women who attending the ANC at University Tripoli hospital, the results revealed that 182(53.2%) of them had poor knowledge, 128 (37.4%) had moderate level and 32(9.4%) had a higher level of knowledge (Figure 1).

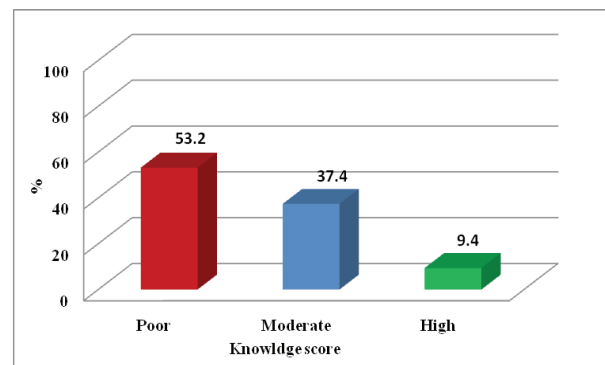
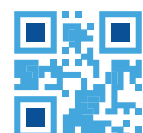


Figure 1: Knowledge score of pregnant women regarding HBV.



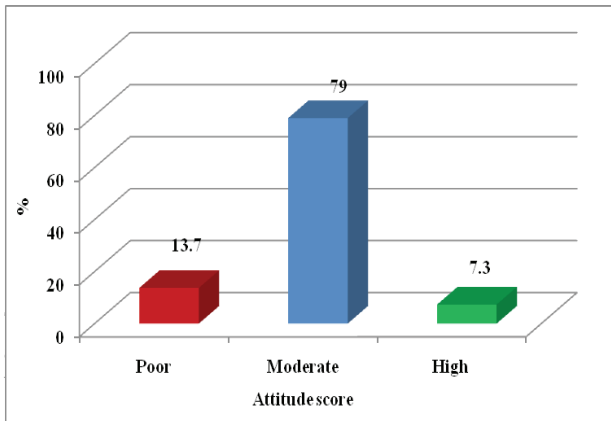


Figure 2: Attitude score of pregnant women regarding HBV.

The relation between knowledge and attitude responses with Socio-demographic characteristics as shown in Table 2, which demonstrated that the higher education level was associated with better knowledge ($P= <0.001$) and attitude scores ($P= 0.04$). There was a significant difference between the occupation and the knowledge scores ($P= 0.014$).

Table 2: Distribution of participants according to demographic characteristics and knowledge, attitude towards HBV.

Character	Favourable knowledge	P-value	Unfavourable attitude	P-value
Age (year)				
<25	22(14.1%)	0.037	45(15.7%)	0.8
25-34	75(48.1%)		146(50.9%)	
35-44	59(37.8%)		92(50.9%)	
45-54	0		4(1.4%)	
Education level				
Illiterate	2(1.3%)	<0.001	9(3.1%)	0.04
Essential	12(7.5%)		27(9.2%)	
Secondary	64(40.5%)		136(46.4%)	
College or above	81(50.9%)		121(41.3%)	
Occupation				
Employment	79(49.4%)	0.014	122(41.5%)	0.75
House wife	66(41.2%)		144(49%)	
Student	15(9.4%)		28(9.5%)	

DISCUSSION

Prevention of both vertical and horizontal transmission is one of the key strategies to reduce the incidence of Hepatitis B. This measure can only succeed if the population has good knowledge and awareness of the infection because it requires comprehensive participation of community members.¹⁶

This study examined the knowledge and attitude of pregnant women attending ANC at Tripoli University Hospital. The results of our study showed that 53.2% of the participants have poor knowledge, 37.4% of them had moderate level, and 9.4% with high knowledge. In comparison with a study carried out by Yankam *et al* in Cameroon in 2017,

documented that (39.8%) had poor knowledge, (38.52%) had good knowledge, and (21.31%) demonstrated excellent knowledge on the transmission and prevention of hepatitis B virus infection.¹⁷

The present findings are in accordance with another study conducted by Bayuh in Ethiopia, showed the overall knowledge of the participants was poor and their attitude and practice were limited.¹⁸

In addition, in a cross-sectional study conducted in China in 2017, only 21% of the participants were able to answer all the general knowledge-related questions correctly.¹⁹

A study in Nigeria conducted by Adeyemi *et al*, that assessed the knowledge of 643 pregnant women about Hepatitis B infection found that 76% of women had inadequate knowledge of HBV infection.²⁰

Other studies conducted in Cameroon²¹, Ghana²² revealed similar results.

Similarly, a population-based knowledge, attitudes, beliefs and practices study in France, indicated a low level of knowledge on the modes of transmission of HBV through sex contact or sharing of needles by injecting drug users.²³

Concerning the relationship between demographic characteristics and KA, the results in the current study demonstrated that the age, occupation, and educational level, were significantly associated with knowledge score of pregnant women regarding HBV transmission and vaccination.

Our study clearly demonstrates that people with higher level of education are more likely to be aware and knowledgeable of HBV. This is not surprising since people who are educated are in a better position to access more sources of information and learn more about HBV.

This finding is similar with the results of Ngaira *et al* in Kenya that reported the women showed a low level of HBV awareness (12.2%) and higher education attainment had a strong association with HBV infection awareness.²⁴

In our study, younger women who aged <35 years (62.2%) were more likely to have correct knowledge than those aged 35-54 years ($P<0.05$). In accordance with the finding of Noreen *et al* study, that found younger age group (14-35 years) were have correct knowledge than those aged 35-49 years ($P<0.005$); also he reported that twice as many women with a higher and matriculation level of education had correct knowledge than did illiterate women ($P< 0.01$).²⁵

In the current results, there was a significant difference between occupation of respondents and level of knowledge ($P = 0.014$), employed women had higher frequency of correct knowledge than housewives; similar finding reported by Noreen *et al*, those who were employed in government service or private business tended to have better knowledge than housewives and the jobless.²⁵

The great majority of the respondents (86.2%) showed a favourable attitude towards HBV that 87.4% of the pregnant women accept HBV screening, 79.2% of them agree to provide care for infected person, but only 27.8% of respondents agree to use condom for safe sex practice.

Study limitation:

Small sample size, inadequate financial resources and time constraints limited the scope of the study.



CONCLUSION

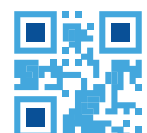
Knowledge and awareness of HBV among pregnant women in Libya, is low and this could have the potential to hamper effective HBV prevention and control in Libya.

ACKNOWLEDGEMENT

Research team would like to acknowledge and thank all participants, Dr. Liala Dabag, Sara Elsaid, Farida Shakshouki for their work in data collection, and the nursing staff of the ANC in Tripoli Medical Centre for their collaboration, as well as to the National Centre for Disease Control-Libya. In addition, the team would like to extend our acknowledgement and sincerely thank to Dr. Hussin ben Othman for his support, guidance and supervision, Dr. Fituri Caballa for his encouragement and support for the preparation of the study proposal through the final write-up of the research paper, without them, this research would not have been able to be achieved. Furthermore, the team would like to express their gratitude to the families for their support.

REFERENCES

- Schweitzer A, Horn J, Mikolajczyk RT, Krause G and Ott JJ. (2015) Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013, *Lancet* **386**(10003), 1546-1555.
- GBD (2013) Mortality and causes of death collaborators (2015) Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the global burden of disease study 2013, *Lancet* **385**(9963), 117-171.
- Perz JF, Armstrong GL, Farrington LA, Hutin YJ and Bell BP. (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide, *J Hepatol*. **45**(4), 529-538.
- Navabakhsh B, Mehrabi N, Estakhri A, Mohamadnejad M and Poustchi M. (2011) Hepatitis B Virus Infection during Pregnancy: Transmission and prevention, *Middle East Journal of Digestive Diseases*. **3**(2), 92-102.
- WHO (2014) Hepatitis B Factsheet N°204. 2014. <http://www.who.int/mediacentre/factsheets/fs204/en/>
- Health protection surveillance center. EMI Guidelines (2016) Hepatitis B virus epidemiology and transmission risks Hepatitis B virus: epidemiology and risk transmission. Available at: <https://www.hpsc.ie/a-z/EMIToolkit/appendices/app21-26.pdf>
- Kwon SY and Lee CH. (2011) Epidemiology and prevention of hepatitis B virus infection, *The Korean Journal of Hepatology* **17**(2), 87-95.
- Lee C, Gong Y, Brok J, Boxall EH and Gluud C. (2006) Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis, *BMJ*. **332**, 328-336.
- Yao JL. (1996) Perinatal transmission of hepatitis B virus infection and vaccination in China. *Gut*. **38**(2), S37-S38.
- Jonas MM. (2009) Hepatitis B and pregnancy: an underestimated issue, *Liver International* **29**(1), 133-139.
- Hamborsky J, Kroger A, Wolfe S, eds (2015) Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Washington D.C. Public Health Foundation.
- Obata H, Hayashi N, Motoike Y, et al. (1980) A prospective study on the development of hepatocellular carcinoma from liver cirrhosis with persistent hepatitis B virus infection. *International Journal of Cancer Journal International du Cancer* **25**(6), 741-747.
- Beasley RP, Hwang LY, Lin CC and Chien CS. (1981) Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan, *Lancet* **2**(8256), 1129-1133.
- Hyams KC, Okoth FA, Tukei PM, et al. (1989) Epidemiology of hepatitis B in eastern Kenya, *Journal of Medical Virology* **28**(2), 106-109.
- Rajamoorthy Y, Taib NM, Munusamy S. et al. (2019) Knowledge and awareness of hepatitis B among households in Malaysia: a community-based cross-sectional survey, *BMC Public Health* **19**, 47.
- Yankam BM, Anye CS, Nkfusai NC, Shirinde J and Cumber SN. (2019) Knowledge and practice of pregnant women and health care workers on hepatitis B prevention in the Limbe and Muyuka health districts of the south west region of Cameroon, *Pan Africa Medical Journal* **33**, 310.
- Bayuh F. (2014) Prevalence of Hepatitis B surface antigen and KAP towards HBV infection, among pregnant women attending selected antenatal Clinics in Addis Ababa, Ethiopia [thesis]. Addis Ababa University; 2014. [accessed 23 July 2019] Available at: [http://etd.aau.edu.et/bitstream/handle/123456789/4712/Fikremariam Bayuh.pdf](http://etd.aau.edu.et/bitstream/handle/123456789/4712/Fikremariam%20Bayuh.pdf)
- Han Z, Yin Y, Zhang Y, Ehrhardt S, Thio CL, Nelson K E, et al. (2017) Knowledge of and attitudes towards hepatitis B and its transmission from mother to child among pregnant women in Guangdong Province, China, *PLoS ONE* **12**(6), e0178671.
- Adeyemi AB, Enabor O, Ugwu IA, Bello FA and Olayemi O (2013) Knowledge of hepatitis B virus infection, access to screening and vaccination among pregnant women in Ibadan, Nigeria, *Journal of Obstetrics and Gynaecology* **33**(2), 155-159.
- Frambo Besong Andreas A JA, Fon Peter Nde and Ndumbe Peter Martins (2014) Prevalence of HBsAg and knowledge about hepatitis B in pregnancy in the Buea Health District, Cameroon: a cross-sectional study, *BMC research notes* **7**, 394.
- Mkandawire P, Richmond C, Dixon J, Luginaah IN and Tobias J. (2013) Hepatitis B in Ghana's upper west region: a hidden epidemic in need of national policy attention, *Health & place* **23**, 89-96.
- Brouard C, Gautier A, Saboni L, et al. (2013) Hepatitis B knowledge, perceptions and practices in the French general population: the room for improvement, *BMC public health* **13**, 576.
- Ngaira JA, Kimotho J, Mirigi I, Osman S, Ng'ang'a Z, Lwembe R, et al. (2016) Prevalence, awareness and risk factors associated with Hepatitis B infection among pregnant women attending the antenatal clinic at Mbagathi District Hospital in Nairobi, Kenya, *Pan Afr Med J*. **24**, 315.
- Noreen N, Kumar R and Shaikh BT. (2015) Knowledge about hepatitis B vaccination among women of childbearing age: a cross-sectional study from a rural district of Punjab, Pakistan, *EMHJ* **21**(2), 129-133.



Safety Profile of Biologics at Pediatrics Rheumatology Clinic, at Children Hospital in Tripoli City, (2009-2019)

Soad Hashad^{@1,2}, Iman Almislati², Majeda Altfeel², Halah Etayari², Zuhrah Awahidah² and Aya Etwati²

¹Department of Pediatric, Faculty of Medicine, University of Tripoli

²Pediatric Rheumatology Clinic, Tripoli Children Hospital

Received 8 September 2019/Accepted 6 December 2019

ABSTRACT

The advent of biological drugs has revolutionized the management of various pediatric rheumatologic diseases, primarily juvenile idiopathic arthritis (JIA). These drugs enable better disease control and prevent or retard damage due to active disease in a substantial number of children. The study conducted to evaluate the risk of infection, (mild and severe), anaphylaxis, malignancy and autoimmunity among pediatric rheumatology patients treated with biologics. This was a case series retrospective study; carried out in Rheumatology unit Tripoli Children Hospital, including all children receiving biologics. The six biologics studied were etanercept, adalimumab, anakinra, infliximab, rituximab and tocilizumab. Medical records were reviewed demographic data; information related therapy, infections, anaphylaxis, malignancy, autoimmune diseases, and reason of discontinuation were collected. Data analyzed by using the Statistical Program for Social Sciences version 16.

All 92 patients treated with six different biologics between 2009 and 2019 were included, 53(58%) were females. The majority of patients had JIA 66(71.7%). Most common side effect was mild to moderate infection in 49 patients (33.3%) in all biologics, and no cases of TB or meningitis. The most common type of infection was mild upper respiratory tract infections, pneumonia that does not require hospitalization. Injection site reaction only noted in 16 patients treated with anakinra.

New onset uveitis in two patients in Etanercept group, hypersensitivity reaction was recorded in 4(4.3%) patients. Abnormal LFT in form of high transaminase or bilirubin registered noted in 17 patients most of them (75%) among cases receiving Tocilizumab. Biologics discontinued in 47(51%) of the cases for different reasons, remission and inefficacy were most common causes.

The safety profiles of the six available studied biologics, are highly acceptable and encouraging. However, more long-time data is needed for severe adverse events.

Keywords- JIA; Biologics; Rheumatology; Pediatrics; Safety.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) affects between 1:1000-1:2000 children, untreated JIA can last well into adulthood, causing significant long-term functional impairment.¹

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of unknown aetiology in childhood and predominantly presents with peripheral arthritis. The disease is divided into several subgroups, according to demographic characteristics, clinical features, treatment modalities and disease prognosis.² International League of Associations for Rheumatology (ILAR) classified JIA to seven subtypes: systemic (SoJIA), oligoarthritis (oligoJIA), rheumatoid factor positive poly articular (RF+ve poly JIA), rheumatoid factor negative polyarthritis (RF-ve poly JIA), Enthesitis related juvenile (ERA) psoriatic (JPsa) and undifferentiated arthritis.²

Improved understanding of the pathogenesis of rheumatoid arthritis has led to the development of various rheumatoid arthritis (RA) treatments. The current therapies for RA are divided into four categories: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, non-biologic disease-

modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs.³

Biologic agents are molecules that specifically target cytokines or cell surface antigens and different from traditional immunosuppressive or disease-modifying anti-rheumatic drugs (DMARDs), as they target to and selectively block only one inflammatory pathway such as tumor necrosis factor (TNF- α) blockers (etanercept, adalimumab, infliximab), interleukin-1 (IL-1) inhibitors (anakinra), IL-6 receptor blockers (tocilizumab), and anti-CD20-antibodies (rituximab). In contrast traditional DMARDs act on multiple pathways and cause generalized immune suppression.^{4,5}

With the increasing use of anti-TNF agents, a number of common concerns have arisen. One of which is the increased risk of infection, particularly tuberculosis; fungal infections, including histoplasmosis; and other opportunistic infection. Infusion and injection reactions, the occurrence and aggravation of infections, the occurrence of a second autoimmune disease, including uveitis, psoriasis, chronic inflammatory bowel disease, multiple sclerosis, diabetes mellitus, and the development of



malignancies are major concerns regarding treatment with biologics.⁶

Biological agents have been shown to be efficient and safe in JIA patients, despite reports of increased frequency of infections that sometimes require hospitalization and sporadic reports of autoimmune diseases. There is some evidence that treatment with TNF blockers could increase the risk of malignancy in children. However, a clear causal relationship has not been established since underlying illnesses and the use of concomitant immunosuppressants bear a risk of malignancy as well.²

The efficacy of BAs has now been well demonstrated in various subtypes of juvenile idiopathic arthritis (JIA)⁷⁻⁹, indifferently pediatric rheumatological disease; however, there are only a few observational studies that have been conducted in children with rheumatic diseases to evaluate the risk of infection and serious side effect.^{10,11} Hence, we conducted this study to evaluate the risk of infection, (mild and severe), anaphylaxis, malignancy and autoimmunity among our patient.

MATERIALS AND METHODS

This was a case series, retrospective study, conducted in Rheumatology unit at Tripoli Children Hospital. A ninety two patients treated with the six different biologics, between 2009 and 2019 were included in the study, receiving biologics for any diagnosis in clinic mainly JIA subtypes, systemic lupus erythematosus (SLE), Behçet disease, chronic uveitis, childhood vasculitis, autoinflammatory disease, and inflammatory bowel disease. The six biologics studied were etanercept, adalimumab, anakinra, infliximab, rituximab and tocilizumab. A case sheet was used to collect the information about the patients from the medical record of the infusion unit. Medical records were reviewed for age at diagnosis, age at starting of treatment, disease phenotype, therapy, infusion dates, dose, and intervals, duration of disease before start biologics, previous steroids and disease modifying drugs, failed previous biologics and Co-treatment with methotrexate, or other disease modifying agents.

Outcomes measure included adverse events: severe adverse events (serious side effect anaphylactic reaction, serious infection, death) or other milder form of side effect, macrophage activating syndrome (MAS), development of autoimmune disease, tolerability and reason of discontinuation.

Statistical analysis was done by using the Statistical Program for Social Sciences SPSS version 16. Descriptive statistics were used and the results are presented as frequencies, means ± standard deviation, and percentages.

RESULTS

Total number of cases attending rheumatology clinic at Tripoli children hospital were 749 children, of which 241(32%) were JIA, and 508(68%) were non JIA. Total number of cases who received biological drugs was 92 children. Out of 92 cases that treated with biological drugs, there were 39(42%) males and 53(58%) females; male to female ratio was 1:1.4. Most of the treated patients 37 (40.2%) were diagnosed after 10 years of age, and 39.1% were diagnosed between 4-10 years of age.

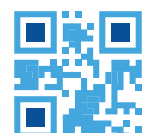
About half (56.5%) of the patients started the treatment after 10 years of age, and 8.7% started the treatment less than 4 years of age (Table 1).

Among 92 cases, JIA was reported in 66(71.7%) of them. Systemic juvenile idiopathic arthritis was most frequent subtype of JIA 26(28.3%), followed by seronegative polyarticular juvenile idiopathic arthritis 12(13%) and enthesitis-related arthritis 11(12%). Chronic uveitis was reported in 7(7.6%) of the cases and 6 (6.5%) of patients with childhood vasculitis. Concerning the duration of disease before biologics, 54 (58.7%) patients treated with biologics within first 2 years of disease; while 38 (34.8%) patients were received the biologics after 2 years of diagnosis (Table 1).

Table 1: Clinico-demographic characteristics of the cases

Character	No.	%
<i>Age at diagnosis</i>		
<4	19	20.7
4-10	36	39.1
>10	37	40.2
<i>Age at starting treatment</i>		
<4	8	8.7
4-10	32	34.8
>10	52	56.5
<i>Sex</i>		
Male	39	42
Female	53	58
<i>Disease type:</i>		
JIA	66	71.7
Non JIA	26	28.3
<i>JIA subtype:</i>		
Oligoarticular JIA	9	9.8
Polyarticular seropositive JIA	5	5.4
Polyarticular seronegative JIA	12	13
SOJIA	26	28.3
ERA	11	12
JPsA	2	2.1
Undifferentiated	1	1.1
<i>Non JIA:</i>		
SLE	4	4.3
Behçet disease	2	2.2
Chronic uveitis	7	7.6
Childhood vasculitis	6	6.5
Auto inflammatory disease	5	5.4
Inflammatory bowel disease	2	2.2
<i>Duration of disease before starting treatment</i>		
≤ 2 years	54	58.7
>2 years	38	41.3

ERA: Enthesitis-related arthritis, soJIA : systemic-onset JIA , JPsA : juvenile psoriatic arthritis



According to biologics used; 37(40%) received etanercept, 9(10%) received adalimumab, 16(17%) received anakinira, 11(12%) received infliximab, 7(8%) received rituximab and 12(13%) received tocilizumab (Figure 1).

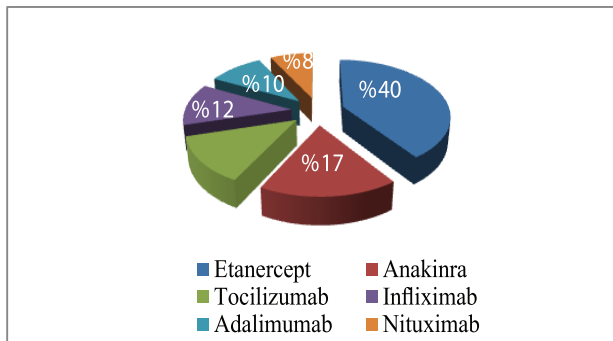


Figure 1: Types of biologics prescribed to the cases

Eleven patients used more than one biologics; six patients used 3 biologics and 5 patients used 2 biologics which represents

6.5%, 5.4% from total patients respectively.

The most commonly used drugs with biologics are Methotrexate (MTX) (69.6%), and prednisolone (46.7%) (Figure 2).

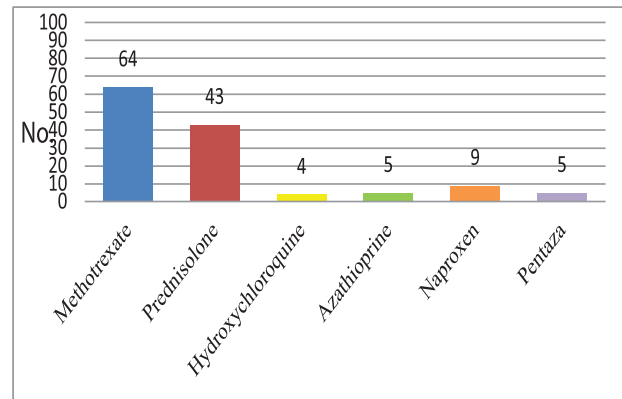


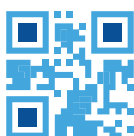
Figure 2: Concurrent treatment with biologics in study population.

Table 2: Adverse drug reactions to biologics among study population

Side effect	Etanercept	Adalimumab	Anakinira	Infliximab	Rituximab	Tocilicumab	Total
	Number %	Number %	Number %	Number %	Number %	Number %	Number %
Infection	22 59.4%	4 44.4%	7 43.75%	8 72.7%	6 85.7%	10 83%	49 53.2%
New onset uveitis	2 5.6%	0 0%	0 0%	0 0%	0 0%	0 0%	2 2.2%
Hypersensitivity reaction	0 0%	0 0%	0 0%	2 18.2%	1 14.3%	1 8.3%	4 4.3%
Injection site reaction	0 0%	0 0%	16 100%	0 0%	0 0%	0 0%	16 17.4%
New ANA positivity	1 2.8%	0 0%	0 0%	0 0%	0 0%	0 0%	1 1.1%
Abnormal LFT	0 0%	4 44.4%	3 18.75%	1 9.1%	0 0%	9 74.9%	17 18.5%
High cholesterol	0 0%	1 5.9%	0 0%	0 0%	0 0%	2 16.7%	3 3.3%
Neutropenia	0 0%	0 0%	0 0%	2 18.2%	0 0%	3 25%	5 5.4%
Lymphopenia	0 0%	0 0%	0 0%	0 0%	1 14.3%	0 0%	1 1.1%
Thrombocytopenia	0 0%	1 5.9%	0 0%	2 18.2%	0 0%	2 16.7%	5 5.4%

Table 3: Reasons of discontinuation of biologics

Reason for discontinuation	Remission	Inefficacy	Infection	Poor compliance	MAS	Anaphylaxis
Etanercept	8	4	1	1	0	0
Adalimumab	5	3	1	0	0	0
Anakinira	12	3	0	0	1	0
Infleximab	0	1	0	0	0	2
Rituximab	0	0	2	0	0	0
Tocilizumab	0	0	0	2	1	0
Total	25(53%)	11(23.4%)	4(8.5%)	3(6.3%)	2 (4.3%)	2(4.3%)



The most commonly reported side effect was mild to moderate infection, which occurred in 49(53.2%) of the treated patients then abnormal liver function tests (LFT), occurred in 17(18.5%) of the treated patients; injection side reaction 16(17.4%) which documented only with anakinra administration. Most common side effects with administration of Etanercept were infection and new onset uveitis. Hypersensitivity reaction was noted with Infliximab, Rituximab and Tocilizumab use. There were no reported malignancies (Table 2).

The infections that reported are: 27 episode of upper respiratory tract infection (URTI), 8 episodes of pneumonia, 5 episodes of varicella, 3 episodes of gastroenteritis, 3 episodes of urinary tract infection (UTI), 3 episodes paronychia and 2 episodes of valvovaginitis.

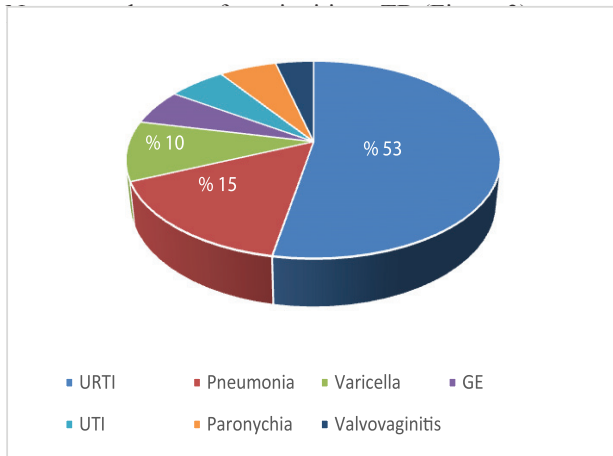


Figure 3: Types of infections with biologics use.

Biologics were discontinued in 47(51%) of the cases for different reasons: 25(53%) due to disease control, 11(23.4%) were non-effective, 4(8.5%) due to infections, 3(6.3%) poor compliance, 2(4.3%) because of macrophage activating syndrome, and 2 patient developed sever anaphylaxis (Table 3).

DISCUSSION

The advance in biologic therapeutics over the past 15 years has led to marked improvement in JIA treatment. In the biological era, the rate of joint damage decreased, and achieved disease remission increased with an increased number of patients with inactive disease. Despite the promising results of these medications, the blockade of important immunological pathways necessitates detailed safety monitoring.²

The study included 92 cases, with female to male ratio of 1.4:1. The most used drug is Etanercept, which reflect its indication for more common subtypes, and its practical S/C weekly administration, which is in accordance with Bethencourt Baute et al results.¹² Followed by Anakinra and tocilizumzb, and infliximab. Eleven of the patients used more than one biologics due to non-efficacy, side effect, or non-availability of previous biologics.

Regarding subclasses of JIA, the most common are systemic onset JIA followed by rheumatoid factor seropositive poly JIA which reflect disease severity and less response to methotrexate in these subclasses. For non JIA group, biologics used as third line for sever disease refractory to standard therapy, and primary vasculitis, BD and idiopathic uveitis are the most common indication consequently.

In general, with the six used biologics, the rates of serious adverse events (AES) were low and No deaths occurred with all drugs, which is comparable with Dutch national biologics registry.⁴

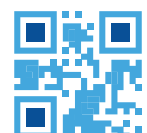
Anaphylaxis reaction occurred in four patients with intravenous biologics and, two on infliximab; sever enough to discontinue the drug. The other two mild allergic reactions and the drug continued. Injection site reaction, in form of erythema and itching at site of S/C injection, documented in all Anakinra treated patients which can be minimized by modifying injection technique;and not documented in other S/C drugs. Our patients are BCG vaccinated and screened annually for all biologics.

No cases of tuberculosis or malignancy were detected, similar finding was reported by Tarkiainen et al.¹⁰ Most common side effect documented is infection in 1-2 episodes per patient per year, URT infections were the most common documented infection; one patient got swine influenza treated with antiviral. In this study, the frequency of mild infections was higher on etanercept or infliximab than on adalimumab, which is in accordance with study of Tarkiainen et al.¹⁰

Food and Drug Administration (FDA) had added a boxed warning with regard to the possible increased risk of malignancy, especially lymphoma in children treated with anti-TNF- agents. There was no malignancy among treated patients after 10 years follow-up, which is compatible with ZahediNiakiet al, and Beukelmanet al studies; did not find an increased incidence of malignancy in patients with JIA children.^{13,14} One girl on adalimumab developed recurrent axillary lymphadenitis and abscess which proofed late manifestation of inherited BD rather a complication of biologics. TNF antagonist therapy has been rarely associated with SLE-like syndromes and antibody syndrome, None of the studied patients developed autoimmune disease like thyroid, celiac, or psoriasis.

Treatment with etanercept does not prevent the onset of uveitis in JIA patients, it is still debatable whether etanercept contributes to the occurrence of uveitis⁴. In present study one girl on etanercept developed new onset uveitis after 3 months of etanercept treatment, but she was a young, with oligoJIA and positive ANA which all considered risk factors to develop uveitis. No flare up of old uveitis in studied patients were noted, this comparable with finding in other studies suggest that etanercept does not cause flare up of uveitis.⁴

Although Guillain-Barre syndrome and optic neuritis were developed in patients identified from the FDA



database. But in the study group where neither multiple sclerosis nor Guillain Barre syndrome were documented, which is comparable in a registry run by PRCSG, where in North America where no case of demyelination disease was documented.⁵

The biologics discontinued in 47 (51%) patients in current study. Remission was the first leading reason for discontinuation of a biologic agent, which is inconsistent with Horneff et al study, where the most common reason for discontinuation was poor efficacy or unsatisfactory response. ¹¹our results are comparable with the Biologics and New Drugs Registry of the British Society for Pediatric and Adolescent Rheumatology (BSPAR); that published the reasons for discontinuation of etanercept therapy, where 100 (20.7%) discontinued etanercept, 9 due to disease control and 88 because of treatment failure (53 due to inefficacy, 14 due to noncompliance and 21 due to adverse events).¹⁵

CONCLUSION

With the six used biologics, no severe side effect, no deaths, and no malignancies. The most frequent side effects were mild to moderate infection, which did not require hospitalizations, and no cases of TB or meningitis. The safety profiles of the six available studied biologics, are highly acceptable and encouraging. However more long-time data is needed for severe adverse events such as, autoimmune events, response to vaccination or malignancies.

RECOMMENDATIONS

More studies on the withdrawal of biologics and the rates of sustained remission of drugs will be needed. In addition, pharmacogenomics will help in more accurately predicting those children who will respond to a particular biologic, require long-term medication or develop major side effects due to a particular drug.

REFERENCES

1. Stoll ML and Gotte AC. (2008) Biological therapies for the treatment of juvenile idiopathic arthritis: Lessons from the adult and pediatric experiences. *Biologics, Targets & Therapy* **2**(2), 229-252.
2. Barut K, Adrovic A, Şahin S and Kasapçopur Ö. (2017) Juvenile Idiopathic Arthritis, *Balkan Med J.* **34**(2), 90-101.
3. Quan LD, Thiele GM, Tian J and Wang D. (2008) The Development of Novel Therapies for Rheumatoid Arthritis, *Expert Opin Ther Pat.* **18**(7), 723-738.

4. Consolaro A and Ruperto N (2017) Biologic response modifiers in pediatric rheumatology. In: Sawhney S, Aggarwal A [Eds.]. *Pediatric Rheumatology: A Clinical Viewpoint*. Springer Singapore, p. 77,78,80
5. Swart JF, de Roock S and Wulffraat NM. (2013) What are the immunological consequences of long-term use of biological therapies for juvenile idiopathic arthritis?, *Arthritis Res Ther.* **15**(3), 213.
6. Ali T, Kaitha S, Mahmood S, Ftesi A, Stone J and Bronze MS. (2013) Clinical use of anti-TNF therapy and increased risk of infections, *Drug Healthc Patient Saf.* **5**, 79-99.
7. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner J B, Tenbrock K, et al. (2015) Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study, *Arthritis Rheumatol.* **67**(8), 2240-2249.
8. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. (2015) Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial, *Ann Rheum Dis.* **74**(6), 1110-1117.
9. Ramanan AV, Dick AD, Jones AP, Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. (2017) Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis, *N Engl J Med.* **376**(17), 1637-1646.
10. Tarkiainen M, Tynjälä P, Vähäsalo P and Lahdenne P. (2015) Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting, *Rheumatology (Oxford).* **54**(7), 1170-1176.
11. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. (2016) Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab, *Arthritis Res Ther.* **18**(1), 272.
12. Bethencourt Baute JJ, Sanchez-Piedra C, Ruiz-Montesinos D, Medrano San Ildefonso M, Rodriguez-Lozano C, Perez-Pampin E, et al. (2018) Persistence and adverse events of biological treatment in adult patients with juvenile idiopathic arthritis: results from BIOBADASER, *Arthritis Res Ther.* **20**(1), 227.
13. Zahedi Niaki O, Clarke AE, Ramsey-Goldman R, Yeung R, Hayward K, Oen K, et al. (2016) Malignancy incidence in 5294 patients with juvenile arthritis, *RMD Open* **2**, e000212.
14. Beukelman T, Haynes K, Curtis JR, Xie F, Chen L, Bemrich-Stolz CJ, et al. (2012) Safety Assessment of Biological Therapeutics Collaboration. Rates of malignancy associated with juvenile idiopathic arthritis and its treatment, *Arthritis Rheum.* **64**(4), 1263-1271.
15. Habibi S and Ramanan AV. (2012) Review of biologics in children with rheumatic diseases, *Int. J. Clin. Rheumatol.* **7**(1), 81-93.



Medical Students' Absenteeism: Magnitude of the Problem and Associated Factors

Halima Dau Buni¹, Entisar Abukenda², Khaled Abuaien¹, Yousef Jabira¹ and Maha Zaid¹

¹Department of Family and Community Medicine, Faculty of Medicine, University of Tripoli

²Department of Family and Community Medicine, Faculty of Medicine, University of Al-Zawia

Received 4 July 2019/Accepted 13 October 2019

ABSTRACT

Frequent absence from the classes leads to inadequate student learning and poor performance in the exams. The problem of University students' absenteeism is increasing, and data about its magnitude and the associated factors at Faculty of Medicine at Tripoli University is lacking. Hence, the study conducted to determine the prevalence of and the main factors associated with medical students' absenteeism at Faculty of Medicine at University of Tripoli during the academic year 2018/2019.

A descriptive cross-sectional study conducted over a period of one month (January,2019). Undergraduate medical students of both sexes and from all year groups of study were included using stratified random sampling technique. Data was collected using a pre-structured, semi open-ended questionnaire. The questions were classified into 3 sections; student-related, college-related and lecturer-related factors for absenteeism. Data was analyzed using the SPSS Version 16. Likert scale has been used to measure the students' attitude. The total sample was 1,497 students, 490 males (32.7%) and 1,007 females (67.3%). The prevalence of absenteeism was 89%. Most students have missed ≥ 9 classes (55%). College-related factors showed the most significant association (high Likert scale rank, mean = 3.72, SD = 0.80). Student-related and lecturer-related factors were also significant but with a moderate rank (mean = 2.72, SD = 0.55 and mean = 3.35, SD=0.77, respectively). Absenteeism is highly prevalent among medical students at Tripoli University. College-related factors were the most significant factors associated with absenteeism.

Key words- Absenteeism; Medical students; Absenteeism related factors,; Problem-based learning; Lectures.

INTRODUCTION

Student absenteeism has been defined as "the frequent absence from classes without any good reason".¹ Frequent absence from the classes leads to inadequate student learning and poor performance in the exams^{2,3}, and also wastes time and reworks for lecturers.⁴ The Professional courses as undergraduate medical education need high theoretical and clinical classes attendance^{4,5}, as those students will be future doctors and will deal with the health and disease of the public.^{2,6,7} Therefore, if a medical student frequently misses the classes and this does not only mean a loss for him/her, but also the whole community², as without getting proper knowledge, clinical skills, and having a good clinical career that satisfies the patient's expectations will be very challenging.² Previously published studies have found that lack of motivation for learning, influence of friends, ill health, family problems^{2,5}, poor relationships with the lecturers, poor teaching

methods^{4,8}, low conducive environment², commitment to job^{4,8}, and the availability of lectures online, on CDs or as audio recordings^{4,9-12} were the most significant contributors to university student's absenteeism.²

Medical students are active contributors to their learning and they must take responsibility for achieving good educational standards through successful completion of each stage of their studies.² Consequently, medical universities set up several measures to ensure students' attendance to achieve their maximum proficiencies.² Dealing with medical student absenteeism and its contributing factors is not a new phenomenon¹², it has been the main concern for the researchers² and has been extensively studied.¹² However, there have been no previously published studies examined the phenomenon of absenteeism and their causes among students at the Faculty of Medicine at University of Tripoli. Thus, this study has been designed to determine the prevalence



of undergraduate medical students' absenteeism at Faculty of Medicine at University of Tripoli during the academic year 2018-2019, and to explore the main factors associated with this phenomenon. With an attempt to find out suggestions, ideas and solutions for absenteeism as reported by the medical students.

MATERIALS AND METHODS

After obtaining a formal permission from the Research and Consulting Department at Faculty of Medicine in University of Tripoli, a questionnaire based cross sectional study was conducted over a period of one month (January, 2019). This study included a total of 1,497 undergraduate medical students from all year groups, who attend Faculty of Medicine in University of Tripoli and who had given consent to participate. Students who had not given consent and were not willing to participate were excluded.

Data was collected from the participating students by using a pre-structured, pre-tested, pre-coded, semi open-ended self-administered questionnaire. The questionnaire included three sections with a total of 37 questions with 5 points likert scale; students-related factors (15 questions), college-related factors (12 questions), and lecturer-related factors (10 questions). To ensure confidentiality and honesty in responses, the questionnaire did not include students' names, study ID and other personal data. Participating students were selected using a stratified random sampling technique. The first stage of sampling involved getting access to student's information from the college's register for all year groups of study (1st year to 5th year). Then a list of students has been sorted out. On the second stage, 300 students have been randomly selected from each stream using a simple random sampling to pick a total sample of 1,497 students. Data was statistically analyzed and interpreted using SPSS V.16. Descriptive statistics including mean, SD and proportion were used to summarize the different variables (quantitative and qualitative). Likert Scale analysis was used to determine the level of significance of association of each question and the overall significance of each of the three sections with absenteeism. The level of significance of association was considered low if the mean score was between 1-2.33, moderate if the mean score was between 2.34-3.66 and high if the mean score was between 3.67-5.

RESULTS

Among the total 1,497 participating students, 490(33%) were males and 1,007(67%) were females, the most frequent age group was 20-22 years (39.7%). The majority of those students (88.1%) were residing in Tripoli. Most of the students (88%) joined the Faculty of Medicine with their own interest, with a smaller number of students joined in under their parent's pressure (12%). Very good and good GAP scores in the last semester were the most frequently reported by the students (37.4% and 32% respectively) (Table 1).

Table 1: Sociodemographic characteristics of participating students

Variable	(%)	Frequency
Sex		
Male	(32.7%)	490
Female	(67.3%)	1,007
Age group		
year 20 >	(15.2%)	227
22 - 20	(39.7%)	594
25 23-	(36.4%)	545
25 <	(8.8%)	131
Year of study		
1 st year	(16.5%)	247
2 nd year	(22.8%)	341
3 rd year	(17.8%)	267
4 th year	(18.2%)	273
5 th year	(24.6%)	369
Residency		
Tripoli	(88.1%)	1,319
Outside Tripoli	(11.9%)	178
Joined the medical college as per choice		
Yes	(88.0%)	1,317
No	(12.0%)	180
Self-reported GAP last semester		
Excellent	(20.1%)	292
Very good	(37.4%)	542
Good	(32.0%)	465
Average	(9.0%)	130
Poor	(1.5%)	22

Regarding the magnitude of absenteeism, the overall prevalence in this study was 89% with more than half of the participating students (55%) had missed more than 9 classes per semester (Figure 1).



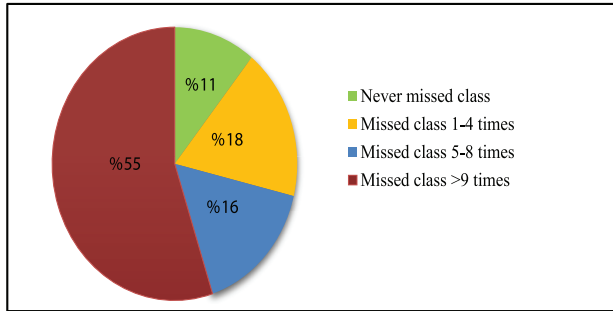


Figure 1: Prevalence of absenteeism among medical students at Faculty of Medicine

Student-related factors have shown an overall moderate significance association with absenteeism (mean score 2.72), with the majority of factors in this section have revealed a moderate significance. However, the factor of “there are those who do not attend the lectures and get high grades” showed a high significant association (mean score 3.95) (Table 2).

Table 2: Student-related factors to medical students’ absenteeism

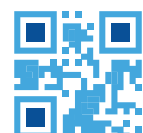
Reason (Students’ related factors)	Frequency (%)	Mean (SD)	Rank
The transportation traffic prevents you from getting on time for lectures	1,467 (98.0%)	3.04 (1.32)	Moderate
Busy with conversations with friends and do not want to go alone for the lecture	1,460 (97.5 %)	2.48 (1.26)	Moderate
Busy in studying a particular subject and do not want to attend other lectures	1,438 (96.1%)	2.95 (1.22)	Moderate
Prefer attending private courses outside the university	1,424 (95.1%)	3.02 (1.42)	Moderate
Currently in work and cannot find time to attend lectures	1,432 (95.7 %)	2.36 (1.25)	Moderate
Prefer home study and listening to lecturer’s recording audios	1,445 (96.5 %)	3.54 (1.24)	Moderate
Can pass without attending lectures	1,443 (96.4 %)	3.48 (1.23)	Moderate
My colleagues do not attend lectures, so I do the same	1,435 (95.9 %)	2.46 (1.25)	Moderate
Have social issues	1,445 (96.5 %)	2.11 (1.16)	Low
Cannot wakeup early, I always go to bed late	1,436 (95.9 %)	2.45 (1.29)	Moderate
Health problems prevent me from attending lectures	1,422 (95 %)	2.09 (1.13)	Low
Prefer to spend time with friends or (fiancé)	1,428 (95.4 %)	2.33 (1.30)	Low

The university is very far from residential place	1,385 (92.5 %)	2.69 (1.31)	Moderate
Not interested in studying medicine, I wish to transfer to another college	1,399 (93.5 %)	1.82 (1.18)	Low
There are those who do not attend the lectures and get high grades	1,429 (95.5 %)	3.95 (1.19)	High
Overall		2.72 (0.55)	Moderate

On the other hand, college-related factors have shown an overall high significance association with absenteeism (mean score 3.72). The top five contributing factors to the absenteeism in this section were poor college facilities (mean score 4.77); lack of modern teaching facilities in classrooms (mean score 4.74); poorly prepared classrooms (mean score 4.43); no enough rest between lectures (mean score 4.38) and all lectures are given in the same classroom (mean score 4.10). The other 7 factors in this section have shown a moderate significant association (Table 3).

Table 3: College-related factors to medical students’ absenteeism

Reason (College’s related factors)	Frequency (%)	Mean(SD)	Rank
Classrooms are not equipped with modern teaching aids	1,438 (96.1%)	4.74 (1.25)	High
Lack of chair and suitable space for each student inside the classrooms	1,429 (95.5%)	2.93 (1.40)	Moderate
The schedule of lectures is not appropriate (e.g., lectures start early and end late)	1,450 (96.9%)	3.37 (1.28)	Moderate
Poor Facilities in the college (e.g., lack of proper bathrooms)	1,439 (96.1%)	4.77 (1.27)	High
There are no places to rest and study at times between lectures	1,420 (94.9%)	3.14 (1.35)	Moderate
All the lectures are given in the same place, making me bored	1386 (92.6%)	4.10 (1.30)	High
The way to the university is not safe	1379 (92.1%)	3.01 (1.51)	Moderate
The College is unable to provide a strict security in the campus.	1396 (93.3%)	3.25 (1.35)	Moderate
Classrooms are not well prepared (no air conditioning, poor ventilation and lighting)	1428 (95.4%)	4.43 (1.34)	High
The college does not take any action regarding students absenteeism	1419 (94.8%)	3.21 (1.29)	Moderate



There is no enough time to rest between the lectures	1449 (96.8%)	4.38 (1.19)	High
Lack of motivation to regular attendance, absence of guidance from the departments and the teachers	1409 (94.1%)	3.36 (1.28)	Moderate
Overall		3.72 (0.80)	High

Whereas lecturer-related factors have also shown an overall moderate significance association with absenteeism (mean score 3.35). Five factors in this section revealed high significant association with absenteeism including, some lecturers do not use modern teaching techniques (mean score 3.98); theoretical lectures do not attract student's interest (mean score 3.93); some teachers do not explain the topics clearly and understandably (mean score 3.91); students entirely do not like the way of teaching and find it not interesting (mean score 3.88) and students feel dissatisfied with teacher's performance in a class (mean score 3.86) (Table 4).

Table 4: Lecturer-related factors to medical students' absenteeism

Reason (Teaching staff's related factors)	Frequency (%)	Mean(SD)	Rank
Feeling dissatisfied with teachers performance in class.	1,449 (96.8%)	3.86 (1.06)	High
Some teachers treat students poorly (e.g. ignore the student's question, never give students choices, never give a break,... etc.)	1,435 (95.9%)	3.35 (1.25)	Moderate
I entirely do not like the way of teaching and find it not interesting	1,452 (97.0%)	3.88 (1.10)	High
Some Teachers do not explain the topics clearly and understandably	1,438 (96.1 %)	3.91 (1.08)	High
Some Teachers do not use modern teaching techniques that improve student's understanding.	1,443 (96.4 %)	3.98 (1.07)	High
Some Teachers do not encourage active learning	1,422 (95.0 %)	3.51 (1.21)	Moderate
Theoretical lectures do not attract student's interest	1,420 (94.9%)	3.93 (1.11)	High
The lectures are very difficult, so I avoid attending to not feel overwhelmed by the lack of understanding	1,384 (92.5%)	2.93 (1.29)	Moderate
Lectures are very easy, attendance is waste of time because I can understand them on my own	1,381 (92.3%)	2.24 (1.17)	Low
Some Teachers do not motivate us for regular attendance, i.e. absence of guidance from departments and teachers	1,409 (94.1%)	3.36 (1.29)	Moderate
Overall		3.35 (0.77)	Moderate

DISCUSSION

Attendance is an essential aspect for the medical students' educational achievement and absenteeism can disrupt the process of learning and teaching.² The present study has shown that absenteeism is highly prevalent (89%) among undergraduate medical students at University of Tripoli, with 55% of participating students reported missed classes more than 9 times. College-related factors showed a high significant association with absenteeism. Particularly, the poor college facilities and poorly equipped classrooms and inadequate rest time between lectures. Although the student's and lecturer-related factors showed an overall moderate association with absenteeism but the majority of the factors included in these sections have shown a high and moderate significant association and should be considered as important contributors to improve medical students' attendance.

Most of the findings from the present studies in relation to student-related factors are consistent with the available evidence, particularly in that many students think that they can pass without attending lectures and they spend their time at work and other extracurricular activities instead of attending lectures.² Also many students reported being busy in studying a particular subject and other exams and do not want to attend other topics' lectures.^{2, 13} Furthermore, the availability of lessons in other sources like CDs and audio records studies^{2,14,15}, and being in work^{1,14} have been also found to be significant contributors similar to the present study. Although lack of interest in studying medical subject has revealed a low association with absenteeism in the present study (mean score = 1.18), however this factor showed significant association in other studies.^{2,14} This inconsistency in findings was also observed regarding student's health problems and social issues which showed significant association^{1,2} contradictory to the present study's finding of low association.

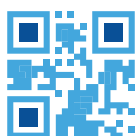
The findings from literature were also consistent with the present study concerning some of the college's and lecturer-related factors; mostly poor college infrastructure^{2,16}, poorly ventilated overcrowded lecture halls, prolonged classes^{2, 16}, lack of clarity about the topic among lecturers while teaching², unfavorable teaching strategies^{14,17,18}, poor teaching skills of lecturers, dissatisfaction about lecturers' teaching methods^{2, 17, 19} and lack of interest in theoretical lectures than the practical and clinical sessions.¹ Therefore, more training should be given to the lecturers in order to improve their teaching methods could help improve attendance.

Limitations

The main limitation of this study is that it was not feasible to study the impact of absenteeism on student's performance as the collected data from students was anonyms and did not include their study IDs.

Strengths

This was the first study that examined the magnitude of the problem of absenteeism and the main factors associated with this problem at Faculty of Medicine in University of Tripoli using a large sample of undergraduate medical students and considering a wide range of contributing factors.



Implications

This study recommends working on the main causes of absenteeism to improve the rate of attendance of medical students in all academic activities. Faculty environment should be improved with provision of proper facilities in class rooms for better learning. Teaching should be more practical and should be prepared in more interesting way. Training programs should be provided to the teaching staff to improve their teaching methodology and to change their orientation from the traditional lecture methods to interactive method. Further research is needed to determine the lecturers' and Faculty decision makers' perspectives toward the phenomenon of medical student's absenteeism.

CONCLUSION

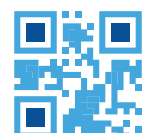
Absenteeism is highly prevalent among undergraduate medical students at University of Tripoli. College-related factors were the most significant factors associated with absenteeism. Particularly, the poor facilities in the college and classrooms. However, there are some student's and lecturer-related should be considered to improve medical students' attendance rates.

ACKNOWLEDGEMENT

The authors express their great gratitude to the medical students who participated in the study and to the intern doctors who helped in data collection and entry.

REFERENCES

1. Qutub MF, Bafail MA, Alomari AS, Azahrani AA, Abuznadah WT, Munshi FM and Alsaywid BS. (2018) Absenteeism among Saudi medical students, *The Egyptian Journal of Hospital Medicine*. **70** (8), 1248-1253.
2. Rao BT, Valleswary K, Durga MS, Nayak P and Rao NL. (2016) Reasons for absenteeism among the undergraduate medical students attending for theory classes in Rajiv Gandhi Institute of Medical Sciences (RIMS) Ongole, Prakasam District of Andhra Pradesh: A Self Review. *Journal of Research and Method in Education*. **6** (4), 11-19.
3. Credé M, Roch SG and Kieszczyńska UM. (2010) Class attendance in college: a meta-analytic review of the relationship of class attendance with grades and student characteristics, *Rev Educ Res*. **80**(2), 272-295.
4. Alghamdi A, Yamani A, Khalil A, Albarkati B, Alrehili O and Salih M. (2016) Prevalence, causes and impacts of absenteeism among medical students at UQU, *Education*. **6**(1), 9-12.
5. Schieffler DA Jr, Azevedo BM, Culbertson RA and Kahn MJ. (2012) Financial implications of increasing medical school class size: does tuition cover cost?, *Perm J*. **16**(2), 10-14.
6. Hidayat L, Vansal S, Kim E, Sullivan M and Salbu R. (2012) Pharmacy student absenteeism and academic performance, *Am J Pharm Educ*. **76**(1), 8.
7. Obeidat S, Bashir A and Abu JW. (2012) The importance of class attendance and cumulative GPA for academic success in industrial engineering classes, *Int J Soc Hum Sci*. **6**, 139-142.
8. Bati AH, Mandiracioglu A, Orgun F and Govsa F. (2013) Why do students miss lectures? A study of lecture attendance amongst students of health science, *Nurse Educ Today*. **33**(6), 596-601.
9. Ruiz JG, Mintzer MJ and Lepizig RM. (2006) The impact of E-learning in medical education, *Acad Med*. **81**(3), 207-212.
10. Davis EA, Hodqson Y and Macaulay JO. (2012) Engagement of students with lectures in biochemistry and pharmacology, *Biochem Mol Bio Educ*. **40**(5), 300-309.
11. Sharmin T, Azim E, Choudhury S and Kamrun S. (2017) Reasons of Absenteeism among Undergraduate Medical Students: A Review, *AKMMC J*. **8**(1), 60-66.
12. Khan YL, Lodhi SK, Bhatti S and Ali W. (2019) Does Absenteeism Affect Academic Performance Among Undergraduate Medical Students? Evidence from "Rashid Latif Medical College (RLMC)", *Advances in Medical Education and Practice*. **10**, 999-1008.
13. BinSaeed AA, Otaibi MS, Ziyadi HG, Babsail AA and Shaik SA. (2009) Association between student absenteeism at a medical college and their Academic Grades, *Med. Sci. Educ*. **19**(4), 155-159.
14. Moorea S, Armstrong C and Pearson J. (2008) Lecture absenteeism among students in higher education: a valuable route to understanding, *J High Educ Policy Manag*. **30**(1), 15-24.
15. Massingham P and Herrington T. (2006) Does attendance matter? An examination of student attitudes, participation, performance and attendance, *J Univ Teach Learn Prac*. **3**(2), 82-103.
16. Dashputra A, Meenal Kulkarni M, Chari S and Date A. (2015) Medical students' absenteeism in class: reasons and remedies. *Journal of Educational Research and Studies*. **3**(1), 24-9.
17. Desalegn AA, Berhan A and Berha Y. (2014) Absenteeism among medical and health science undergraduate students at Hawassa University, Ethiopia, *BMC Medical Education*. **14**, 14-81.
18. Chaudhry SH and Iqbal J. (2019) Absenteeism of Medical Students from Subspecialty Clinical Rotations: A Qualitative Study, *Journal of the College of Physicians and Surgeons Pakistan*. **29** (1), 45-50.
19. Kaushik T, Das R and Saha N. (2015) Attitude of medical students towards the reasons of absenteeism in a medical college of Tripura, *Journal of Dental and Medical Sciences*. **14**(11), 110-112.



Effect of Glycemic Control on Pregnancy out Come in Diabetic Pregnant Women at Obstetric and Gynecological Department in Tripoli-Libya

Hiyam BenRajab^{@1,2}, Fuad Zekri^{1,2} and Weam Najjar¹

¹Department of Gynecology and Obstetrics, Tripoli University Hospital;

²Department of Gynecology and Obstetrics, Faculty of Medicine, University of Tripoli, Libya

Received 3 October 2019/Accepted 16 December 2019

ABSTRACT

Elevated HbA1c is associated with increased risk of adverse pregnancy outcomes including abortion, stillbirth, and congenital abnormalities. The study conducted to assess the association between hemoglobin A1c (HbA1c) and the risk of adverse pregnancy outcomes in diabetic pregnancies.

A cross sectional study included all pregnant diabetic women (251) in a Tripoli University Hospital from January 2017 to January 2018. HbA1c values from first, second and third trimester were collected, and pregnancy outcome was categorized as good (babies surviving the first month of life without major congenital abnormalities) and adverse (spontaneous and therapeutic abortion, stillbirth, neonatal death, or major congenital abnormalities detected within the first month). The frequency of adverse outcomes was calculated according to HbA1c values.

This study identified 251 diabetic pregnant women in the study period. Twenty-seven women with type 1 diabetes (10.4%), 123 gestational (47.3%) and 101 with type 2 diabetes (38.8%) were included in the study. Mean HbA1c early in pregnancy measured in a central laboratory, was higher in the women with an adverse outcome group ($P=0.009$). Second and third trimester HbA1c and mean HbA1c during pregnancy were higher in the women with an adverse outcome group ($P = 0.002$, $P = 0.001$ respectively).

Strong correlation between high HbA1c values and pregnancy adverse outcome specific to every trimester, optimizing glycemic control during pregnancy will reduce these adverse effects.

Keywords- HBA1c; Pregnancy; Outcome.

INTRODUCTION

Diabetes mellitus is one of the most common medical complications of pregnancy; up to 5% of diabetic pregnant women have either pre-existing diabetes or gestational diabetes. Of women who have diabetes during pregnancy, it is estimated that approximately 87.5% have gestational diabetes (which may or may not resolve after pregnancy), 7.5% have type 1 diabetes, and the remaining 5% have type 2 diabetes. The prevalence of type 1 diabetes and especially type 2 diabetes has increased in recent years. The incidence of gestational diabetes is also increasing because of higher rates of obesity in the general population and more pregnancies in older women.¹

Diabetes in pregnancy generates a significant risk to the fetus and the mother. Congenital malformations and perinatal morbidity remain commonly happen when compared with the offspring of non-diabetic pregnancies. Diabetic mothers are always at risk of progression of microvascular diabetic complications as well as early pregnancy loss, pre-eclampsia, polyhydramnios and premature labour.²

There are two common classes of Diabetes Mellitus identified in pregnancy. The first is called pre-gestational diabetes mellitus (diabetes present before pregnancy) that antedates pregnancy and referred to as diabetes mellitus and pregnancy.³ Optimize Glycemic Control: Diabetes ante-natal care should be provided in a special hospitals and the team caring for pregnant women should ideally include a Diabetes Nurse Specialist, Dietician, Diabetologist and an Obstetrician.

The main objective of ante-natal care is to Provide and maintain tight glycemic control and also to monitor the mother for diabetes complications. Tighter glycemic control has effect on maternal and fetal complications. Excellent glycemic control should be continued during the pregnancy, fasting glucose levels of <90-99 mg/dl (5.0-5.5 mmol/l), 1-h postprandial glucose levels of <140 mg/dl (7.8 mmol/l), and 2-h postprandial glucose levels of <120-127 mg/dl (6.7-7.1 mmol/l).⁴ The glycated hemoglobin (HbA1c) reference values were 4.5-6.2% (25.7-44.3 mmol/mol).⁵



Elevated HbA1c is associated with increased risk of adverse pregnancy outcomes including abortion, stillbirth, and congenital abnormalities; Glycosylated hemoglobin (HbA1c) is known to correlate with fetal malformations if elevated during organogenesis.⁶women with high HbA1c were at a higher risk of delivering macrosomicbabies.⁷

The current study conducted to assess the association between hemoglobin A1c (HbA1c) and the risk of adverse pregnancy outcomes in diabetic pregnancies.

MATERIALS AND METHODS

A cross sectional study included all pregnant diabetic women (251) in a Tripoli university hospital (TUH) from January 2017 to January 2018. HbA1c was measured in a central laboratory; values from first, second and third trimester were collected, and pregnancy outcome was categorized as good (babies surviving the first month of life without major congenital abnormalities) and adverse (spontaneous and therapeutic abortion, stillbirth, neonatal death, or major congenital abnormalities detected within the first month). The frequency of adverse outcomes was calculated according to HbA1c values; variables were including Type of diabetes (gestational diabetes /type 1 diabetes / type 2 diabetes), A1c values in the first, second and third trimester of pregnancy, mode of delivery, baby weight, adverse out come and good outcome. Pregnancy outcomes were divided into good (babies surviving the 1st month of life without detected congenital abnormalities) and adverse (composed of stillbirth, neonatal death, major or minor congenital abnormalities detected within the 1st month of life). Data was analyzed using SPSS program version 16. Descriptive statistics including means, standard deviation, frequencies, and percentages were obtained for all variables as appropriate. *P* value < 0.05 considered significant.

Verbal informed consent was obtained from all participants during their follow up at the clinic and data confidentiality was maintained throughout the study and any resulting publication anonymously.

RESULTS

A total 251 diabetic pregnant women were enrolled in present the study. The results showed that 27 (11%) women were with type 1 diabetes, 123(49%) women with gestational diabetes, and 101 women with type 2 diabetes (40%) (Figure 1).

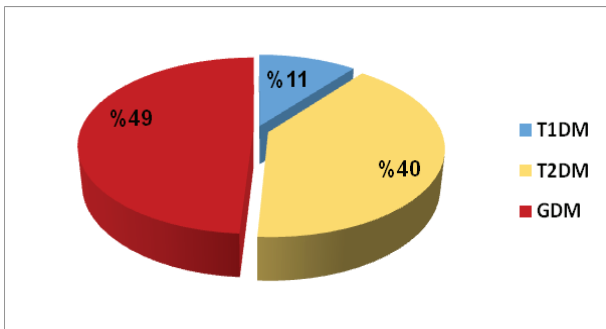


Figure 1: Distribution of patients according to the type of diabetes, TUH, 2016.

The results showed that, 169 cases were in good outcome group, normal vaginal delivery was performed in 79(31.5%) and 172(68.5%) of cases were underwent cesarean section. There was ahiger percentage of caesarian section in both groups. No significant differences were determined between both groups regarding mode of deliver (Table 2).

Table 2: Relation between mode of delivery and pregnancy outcome at TUH 2016

Mode of delivery	Good outcome Group No. (%)	Adverse outcome Group No. (%)
Normal vaginal delivery	59 (35%)	20 (24.4%)
Caesarian section	110 (65%)	62 (75.6%)
Total	169 (100%)	82(100%)

The mean of birth weight of 241 infants was 3677± 711 grams and 162(56.1%) of infants were macrosomic. There were 133 women in first trimester; the mean HbA1c level in First trimester was higher in the women with an adverse outcome group; HbA1c> 7 reported in 76.5% of adverse outcome group. There was a significant difference between HbA1c level and pregnancy outcome (*P* = 0.009) (Table 3).

Table 3: HbA1c value during first trimester and pregnancy outcome at TUH, 2016

HbA1c	Good outcome No. (%)	Adverse outcome No. (%)	Total No. (%)
≤ 6	22 (33.8%)	7(10.3%)	29 (21.8%)
6.1-7	11(17%)	9 (13.2%)	20 (15%)
7.1-8	13 (20%)	18(26.5%)	31(23.3%)
8.1-9	10 (15.4%)	14 (20.6%)	24 (18%)
≥ 9.1	9 (13.8%)	20 (29.4%)	29 (21.8%)
Total	65 (100%)	68 (100%)	133 (100%)

Table 4 showed 78 out of 175 pregnancies in second trimester had adverse outcome; 37% out of them with HbA1c ≤ 7, on other hand 63 % with HbA1c> 7 and HbA1c in Second trimester was higher in the women with an adverse outcome group (*P* = 0.002).

Table 4: HbA1c value during second trimester and pregnancy outcome at TUH, 2016

HbA1c	Good outcome No. (%)	Adverse outcome No. (%)	Total No. (%)
≤ 6	33(34%)	12 (15.4%)	45 (25.7%)
6.1-7	29 (29.9%)	17 (21.8%)	46 (26.3%)
7.1-8	19 (19.6%)	17 (21.8%)	36 (20.6%)
8.1-9	9 (9.3%)	19 (24.3%)	28 (16%)
≥ 9.1	7 (7.2%)	13 (16.7%)	20 (11.4%)
Total	97 (100%)	78 (100%)	175 (100%)

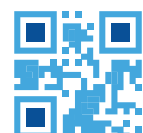


Table 5 showed that HbA1c in third trimester was higher in the women with an adverse outcome group ($P = 0.001$); 100 out of 229 pregnancy had adverse outcome; 54% out of them with HbA1c ≤ 7 on other hand 46% with HbA1c > 7 .

Table 5: HbA1c value during third trimester and pregnancy outcome at TUH, 2016

HbA1c	Good outcome No. (%)	Adverse outcome No. (%)	Total No. (%)
≤ 6	61(47.3%)	32 (32%)	93 (40.6%)
6.1-7	44 (34.1%)	22 (22%)	66 (28.8%)
7.1-8	14 (10.8%)	21 (21%)	35 (15.3%)
8.1-9	8 (6.2%)	14 (14%)	22 (9.6%)
≥ 9.1	2 (1.6%)	11 (11%)	13 (5.7%)
Total	129 (100%)	100 (100%)	229 (100%)

By the end of pregnancy, there were 52 pregnancies recorded with adverse outcome, stillbirth reported in 10(19.2%) of neonates, and neonatal deaths in 3(5.8%) of pregnancies, 19(36.5%) had major congenital anomalies and 20(38.5%) of them had minor congenital anomalies (Table 6).

Table 6: Neonatal outcome at TUH, 2016

Complication	No.	%
Still birth	10	19.2 %
Neonatal death	3	5.8 %
Major congenital anomalies	19	36.5%
Minor congenital anomalies	20	38.5%
Total	52	100%

DISCUSSION

This study report most of patients had gestational diabetes followed by T 2 diabetes and minority have T1 diabetes this supported with Indian study which was carried on 2016 included 325 patients, 54.5% had gestational diabetes, 29.23% had T 2 diabetes and only 16.3% was T1 diabetes.⁵ We noticed more than sixty percent of diabetic women included in our study delivered by cesarean section with no difference in adverse and good outcome in relation to mode of delivery; this going with study in Bahrain 2017 which showed rate of elective caesarean section increased from 12.5% in non-diabetic mothers to 50% in patients with pre-existing diabetes. In cases of allowing a trial of Labour, approximately 70% of patients with pre-existing diabetes had successful vaginal delivery with minimal morbidity.⁸ Macrosomia of infants is one of complications in uncontrolled diabetes in pregnancy, in present study more than 50% were macrosomic. González-Quintero et al.⁹ found that 15.7% women with uncontrolled blood glucose delivered macrosomic babies. In Royal Infirmary, Edinburgh, Scotland, U.K. one study conclude Glycaemic

control in the immediate pre-conception period and early first trimester appears to have a greater influence on birth weight than does glycaemic control during the later weeks of pregnancy.¹⁰

A significant relation between high HbA1c and adverse pregnancy outcome in first, second and third trimesters (P value; 0.009, 0.002, 0.001 respectively) was found in current study, similarly; González-Quintero et al.⁹ found that women with suboptimal glycaemic control had significantly higher rates of adverse neonatal outcome, higher rate of caesarean delivery and higher level of nursery admission. Mane. L et al¹¹ from Barcelona-Spain; they found in a multiethnic population study, an early HbA1c $\geq 5.9\%$ measurement in first trimester identifies women at high risk for poorer pregnancy outcomes independently of gestational diabetes mellitus diagnosis later in pregnancy. Also supported by Capula et al.¹² in Italy showed that HbA1c at diagnosis and before delivery resulted a good predictor of adverse pregnancy outcome. On the other hand, a studies conducted by Nielsen et al^{6,13} reported that, relative risk calculations indicated a highly significant and consistent correlation between HbA1c values above 6.6% and adverse fetal outcome in the first trimester of pregnancy of type 1 mothers, without any indication of a cut-off level below which further improvement in HbA1c was of minor importance.

Our results not supported with Kerssen A. et al¹⁴ study, which proved that although glycaemic control contributes to birthweight in women with type 1 diabetes, the birthweight of an earlier born infant appears to be a much better predictor of the birthweight of a subsequent infant than HbA1c levels during pregnancy. It may, therefore, be used to identify patients at risk of giving birth to a macrosomic infant; so daily home monitoring of glucose levels, rather than HbA1c levels, should be used for assessment of maternal glycaemia during pregnancy. This also supported with USA study¹⁵, which conclude that on the basis of associations with adverse outcomes; HbA1c measurement is not a useful alternative to an oral glucose tolerance test (OGTT) in pregnant women.

In women with preexisting diabetes, early pregnancy HbA1c directly correlates with pregnancy outcomes. Our results showed adverse outcome as still birth, neonatal death, major and minor congenital anomalies correlate with high HbA1c, this agreed by Jensen DM. et al¹⁶ study which found congenital malformation rate increased significantly at A1C above 10.4%, whereas perinatal mortality was increased even at HbA1C below 6.9%.

CONCLUSION

Strong association between high HbA1C values and pregnancy adverse outcome specific to every trimester, optimizing glycaemic control during pregnancy will reduce these adverse effects.

RECOMMENDATIONS

We recommend more studies to express more the correlation between glycaemic control and pregnancy adverse outcome in terms of HbA1c and blood glucose values in pregnant women.



REFERENCES

1. National Institute for health and Care Excellence (2015) Diabetes in pregnancy: management Diabetes in pregnancy: management from preconception to the postnatalfrom preconception to the postnatal period. *NICE guideline*.pp.55 available at: nice.org.uk/guidance/ng3
2. Abourawi F (2006) Diabetes mellitus and pregnancy, *Libyan J Med.* **1**(1), 28-41.
3. Buchanan TA and Xiang A (2005) Gestational diabetes mellitus, *J Clin Invest.* **115**(3), 485-491.
4. Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, et al. (2007) Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus, *Diabetes Care* **30**(2), S251-260.
5. Buhary BM, Almohareb O, Aljohani N, Alzahrani SH, Elkaissi S, Sherbeeni S, et al. (2016) Glycemic control and pregnancy outcomes in patients with diabetes in pregnancy, *Indian J Endocrinol Metab.* **20**(4), 481-490.
6. Nielsen GL, Møller M, and Sørensen HT (2006) HbA1c in Early Diabetic Pregnancy and Pregnancy Outcomes, *Diabetes Care* **29**(12), 2612-2616.
7. Bhavadharini B, Mahalakshmi M M, Deepa M, Harish R, Malanda B, Kayal A, et al. (2017) Elevated glycated haemoglobin predicts macrosomia among Asian Indian pregnant women, *Indian J Endocrinol Metab.* **21**(1), 184-189.
8. Alomran BS, Alammari FH and Dayoub NM (2017) Pregnancy outcomes in relation to different types of diabetes mellitus and modes of delivery in macrosomic fetuses in Bahrain, *Journal of Taibah University Medical Sciences* **12**(1), 55-59.
9. González-Quintero V, Istwan NB, Rhea DJ, Rodriguez LI, Cotter A, Carter J, et al. (2007) The impact of glycemic control on neonatal outcome in singleton pregnancies complicated by gestational diabetes, *Diabetes Care* **30**(3), 467-470.
10. Gold AE, Reilly R, Little J, Walker JD.(1998) The effect of glycaemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM, *Diabetes Care* **21**(4),535-538.
11. Mane. L, Flores-Le Roux J, Benaiges D, Rodriguez M, Marcelo I, Chillaron J, et al. (2017) Role of first-trimester HbA1c as a predictor of adverse obstetric outcomes in a multiethnic cohort, *J Clin Endocrinol Metab.* **102**(2), 390-397.
12. Capula C, Mazza T, Vero R and Costante G (2013) HbA1c levels in patients with gestational diabetes mellitus: relationship with pre-pregnancy BMI and pregnancy outcome, *J Endocrinol Invest.* **36**(11),1038-1045.
13. Nielsen GL, Sørensen HT, Nielsen PH, Sabroe S and Olsen J. (1997) Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies, *Acta Diabetol.* **34**(3), 217-222.
14. Kerksen A, de Valk HW and Visser GHA (2005) Sibling birth weight as a predictor of macrosomia in women with type 1 diabetes, *Diabetologia* **48**,1743-174.
15. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, et al. (2012) Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations of maternal A1C and glucose with pregnancy outcomes, *Diabetes Care* **35**(3), 574-580.
16. Jensen DM, Korsholm L, Ovesen P, Beck-Nielsen H, Moelsted-Pedersen L and Westergaard JG (2009) PericonceptionalA1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes, *Diabetes Care* **32**(6),1046-1048.



Short Communication

ISSN 2077-5628

Maternal and Neonatal Outcome of Spontaneous Preterm Pre Labor Rupture of Membrane

Turaia AbdAlmaksoud^{@1} and Soad Erhuma²¹Department of Gynecology and Obstetrics, Faculty of Medicine, University of Tripoli²Department of Gynecology and Obstetrics, Faculty of Medicine, Sirte University

Received 18 August 2019/Accepted 19 December 019

ABSTRACT

Preterm premature rupture of membrane (PPROM) is a known complication of pregnancy as it is associated with significant perinatal complication. The study aimed to determine the frequency of PPRM among pregnant women at EbenSena Hospital and to study neonatal and maternal outcomes. This prospective longitudinal study was conducted at department of obstetrics and gynecology, EbenSena Hospital in Sirte, between January 2012 and December 2014; 906 cases, who presented with preterm premature rupture of membrane before 37 completed weeks of gestation included in the study. These 906 women were divided into 3 groups according to gestational age (GA), group 1 (28-30 week GA), group 2 (31-33 weeks of GA) and group 3 (34-36 weeks of GA); analysis was done to find the association between PPRM and neonatal, maternal outcomes.

Among 11400 women delivered during the period of the study, 906 women with PPRM identified, the frequency of PPRM was 7.9%, 211(23.3%) were delivered by cesarean section, chorioamnionitis was reported in 140 (15.5%) of the cases and its frequency was more among gestational age group (28-30 weeks), ($P = 0.001$). Most common morbidity among neonates was respiratory distress syndrome 85(9.4%), followed by neonatal sepsis 77(8.5%), and seizure 71(7.8%). The results revealed that 147(16.2%) of neonates developed hypoglycemia, 130(14.3%) hyperglycemia, and 571(63%) hyperbilirubinemia). The occurrence of these complications was more frequently among group of 34-36 weeks gestational age, ($P = 0.0001$). Death rate was 5.3%, with increasing gestational age survival increased to 99.6% at 34-36 weeks of gestation ($P = 0.0001$).

The study results imply that early PPRM is associated with higher rates of perinatal morbidity and mortality.

Keywords- PPRM; Chorioamnionitis; Feto-aterenal outcome.

INTRODUCTION

Preterm premature rupture of membrane (PPROM) is defined as rupture of the fetal membranes with leakage of amniotic fluid occurring before the onset of regular uterine activity prior to 37 completed weeks of gestation. PPRM is a serious complication of pregnancy, occurring in approximately 3-4% of all deliveries.¹ It is one of the leading identifiable causes of prematurity and is responsible for approximately 30% of all preterm deliveries.¹ PPRM is associated with significant perinatal morbidity and mortality that decreases with advancing gestational age at delivery.²

PPROM is multifactorial in nature.^{3,4} Choriodecidual infection or inflammation may cause preterm PROM. A decrease in the collagen content of the membranes has been suggested to predispose patients to pre term PROM.^{4,5} Other risk factors include black patients, lower socioeconomic status smokers, a history of sexually transmitted infections, previous preterm delivery, vaginal bleeding, or uterine distension (e.g., polyhydramnios, multifetal pregnancy). Procedures that may

result in PPRM include cerclage and amniocentesis.⁴

PPROM is associated with an increased risk of serious maternal, fetal, and neonatal morbidities, especially the risks of preterm delivery, and infectious complications, such as respiratory distress syndrome, neonatal sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia and varying degrees of hypoplasia and bronchopulmonary dysplasia.^{6,9}

Several studies have implicated oligohydramnios in patients with PPRM as a significant risk factor for perinatal infection, and fetal distress, cesarean delivery, and neonatal death.⁵

Maternal complications include intraamniotic infection, which occurs in 13%- 60% of women with PROM, placental abruption, and postpartum endometritis⁸ and increased risk of caesarean section are noted.¹⁰

Management of PROM requires an accurate diagnosis as well as evaluation of the risks and benefits of continued pregnancy or expeditious delivery. An understanding of gestational age-dependent neonatal morbidity and mortality



is important in determining the potential benefits of conservative management of preterm PROM at any gestation. Where possible, the treatment of pregnancies complicated by PROM remote from term should be directed towards conserving the pregnancy and reducing perinatal morbidity due to prematurity while monitoring closely for evidence of infection, placental abruption, labor, or fetal compromise due to umbilical cord compression.¹¹

The objectives of the present study were to determine the frequency of PPRM among pregnant women at Eben Sena Hospital in Sirte and to study neonatal and maternal outcomes.

MATERIALS AND METHODS

The present study was prospective longitudinal type, conducted in the Department of Obstetrics and Gynecology at EbenSena Hospital in Sirte. It was included all (906) patients from January 2012 to December 2014, who presented with preterm premature rupture of membrane before 37 completed weeks of gestation. The women were divided into 3 groups according to gestational age [GA], group 1 PPRM (28-30 week) (n=132), group 2 PPRM (31-33 weeks of GA) (n=278) and group 3 PPRM (34-36 weeks of GA) (n=496). Collected data was included age, parity, social status of patients, duration of leaking, past medical and obstetric history.

PPROM were confirmed if on speculum examination, there was amniotic fluid seen draining through the cervical OS. All patients with PPRM were put on conservative management if no signs of infection were present and active management was done if any sign of infection was present.

Maternal and fetal status was closely monitored for development of chorioamnionitis, labour or fetal complications. The criteria for maternal infection was temperature >38 °C with one or more of the following signs, uterine tenderness, fetal or maternal tachycardia or foul smelling amniotic fluid draining per vaginam in absence of any obvious reason for elevated temperature.

If infection was identified, delivery was expedited and the use of broad-spectrum antibiotics was initiated. Administration of Betamethasone 12 mg intramuscularly (2 doses 24 hours apart) for pregnancies less than 34 weeks was recommended.

Maternal and neonatal outcomes were recorded including maternal infection morbidity (endometrium or chorioamnionitis) and major neonatal morbidities (respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), neonatal sepsis (NNS), Pneumonitis, seizure, meningitis) and biochemical complication which include hypoglycemia, hyperglycemia, hyperbilirubinemia, and hyponatremia.

The data were analyzed by descriptive statistics using the statistical package for social science version 16 and the results expressed in descriptive statistics by simple percentages. A *Chi-square* test was used for categorical variables, and a *P* value <0.05 considered as significant.

RESULTS

Among 11400 women delivered during the period of the study, 906 women with PPRM identified, the frequency of PPRM was 7.9%, out of which 132(14.6%) cases were between 28-30 weeks, 278(30.6%) between 31-33 weeks and 496(54.7%) were between 34-36 weeks. In this study, maximum number of women was between 21-37years. The results showed that 695 (76.7%) of cases had normal vaginal delivery (NVD), while 211(23.3%) were delivered by cesarean section (CS), and there was no instrumental delivery. There was a significant difference between mode of delivery and gestational age (*P* = 0001), (Table 1).

Table 1: Mode of delivery according to gestational age

Gestational age	NVD No. (%)	CS No. (%)	Total No. (%)
28-30	78 (59.1%)	54 (40.9%)	132(100%)
31-33	227 (99.6%)	51 (18.3%)	278(100%)
34-36	390 (78.6%)	106 (21.3%)	496(100%)
Total	695(76.7%)	211(23.3%)	906 (100%)

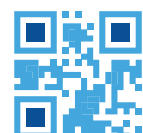
Out of 906 cases, 140 (15.5%) women had maternal complication in the form of chorioamnionitis and its frequency was more among gestational age group (28-30 weeks), *P* = 0001 (Table 2).

Table 2: Maternal morbidity (chorioamnionitis) in relation to gestational age

Gestational age	Chorioamnionitis	No Chorioamnionitis	Total
28-30	78 (59.1%)	54 (40.9%)	132(100%)
31-33	27 (9.7%)	251 (90.3%)	278(100%)
34-36	35 (7.1%)	461 (92.9%)	496(100%)
Total	140 (15.5%)	766(84.5%)	906 (100%)

Among 906 neonates most common morbidity was respiratory distress syndrome(RDS) in 85(9.4%), followed by neonatal sepsis (NNS) in 77(8.5%), seizure in 71(7.8%), while pneumonia, necrotizing enterocolitis (NEC), and meningitis, were 2.3%, 2%, 0.8% respectively (Figure 1).

Most of neonatal morbidities were found at 28-30 weeks gestational age. RDS in 71(53.8%), seizure in 65(49.2%), sepsis in 51(38.6%), necrotizing enterocolitis in 14(10.6%), pneumonia in 12(9%), meningitis in 2(1.5%) babies. While at 34-36weeks, respiratory distress syndromein3 (0.6%), neonatal sepsis in 8(1.6%), seizure in 1(0.2%), no pneumonia and meningitis, *P*= 0.0001 (Figure 1).



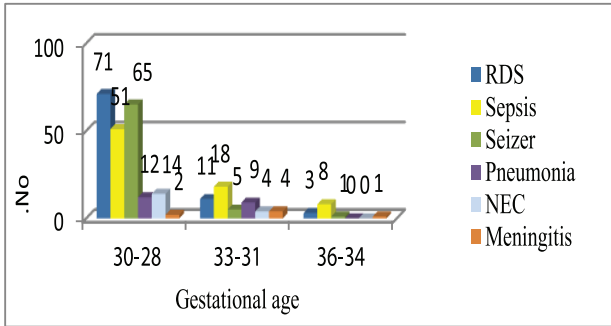


Figure 1: Distribution of neonatal morbidity according to gestational age

Regarding Biochemical complications, results revealed that among 906 neonates, 147(16.2%) of neonate developed hypoglycemia, 130(14.3%) hyperglycemia, 571(63%) hyperbilirubinemia and hyponatremia was reported in 178(19.6%) neonates (Figure 2).

The occurrence of these complications was more frequently among group of 34-36 weeks gestational age, $P = 0.0001$ (Figure 2).

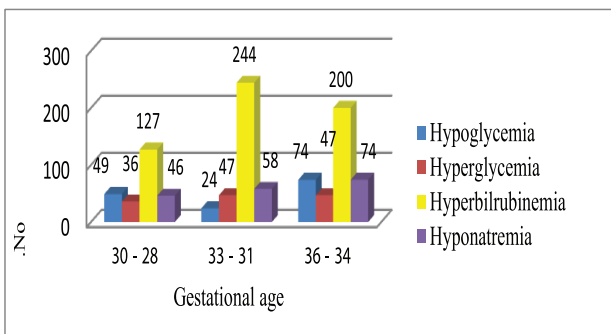


Figure 2: Distribution of biochemical complications according to gestational age.

In this study there were 858(94.7%) alive births and 48(5.3%) were deaths. Maximum neonatal death were in babies belonging to 28-30 weeks of gestation but with increasing gestational age survival increased to 99.6% at 34-36weeks of gestation, $P = 0.0001$ (Figure 3).

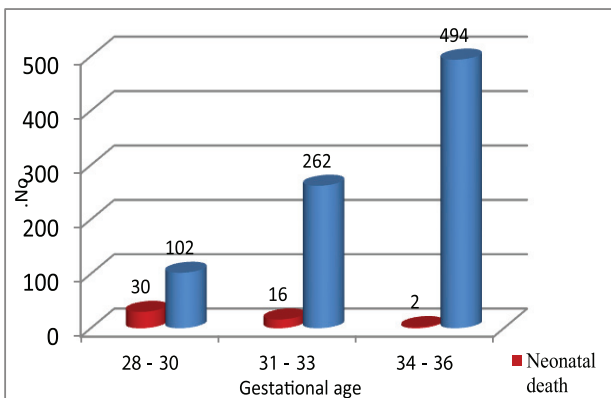


Figure 3: Neonatal outcomes according to gestational age

DISCUSSION

PPROM evaluation and management are important for improving neonatal outcomes. Accurate diagnosis of PPRM requires a thorough history, physical examination and laboratory studies. These would allow for gestational age specific obstetric interventions to optimize perinatal outcome and reduce fetomaternal complications.¹²

The frequency of PPRM in present study was 7.9%. This was higher than that reported by Idrisa et al⁸ (3.2%), Okeke et al¹² (3.3%), and Shukla et al² (1.8%); it is mainly because the EbenSena Hospital was referred center; but it is comparable to range of 3-8% as reported by Egarter *et al.*¹³

Hocq et al¹⁴ study reported that infection is a common complication of PPRM, the clinical chorioamnionitis rate was 30%, but in present study, chorioamnionitis reported in 15.5% of the cases. This finding was consistent with the results of Linehan et al.¹⁵

Cesarean section rate in the current study was 23.3%, when comparing with other studies it lower than that reported by D’souza et al¹⁶ (36%) and by Tavassoli et al¹⁷ (32%).

When PROM occurs, too early, surviving neonates may develop sequelae such as malpresentation, cord compression, oligohydramnios, necrotizing enterocolitis, neurologic impairment, intraventricular hemorrhage, and respiratory distress syndrome.⁴

Early PPRM were at significantly higher risk of adverse outcomes during neonatal period, even the neonatal death rate was higher among those delivered following early PPRM compared with late PPRM (22.7% vs 0.4%). Although the incidence of neonatal complication is high, but comparable to that documented by Elimian et al¹⁸ and Dexter et al.¹⁹

Our results revealed that most of neonatal morbidities were reported among 28-30 weeks gestation, mainly RDS (53.8%), seizure (49.2%), and sepsis (38.6%), in agreement with Shukla et al study².

And RDS was the commonest neonatal complication and it is around 9% at all gestation which equally to result founded by Lieman et al²⁰ and significantly higher among pregnancies delivered at 33 weeks or less. Despite this, high neonatal complication maybe related more closely to the effect of premature birth and sophistication of newborn care unit.

CONCLUSION

PPROM is major complication of pregnancies and an important cause of perinatal mortality and morbidity along with maternal morbidity. Several areas of controversies exist regarding the best approach of management of PPRM. The management of pregnancies complicated with PPRM is individualized, highly controversial, and challenging. Management of PPRM varies according to the gestational age of the fetus, expectant management and immediate delivery are the two potential options in these patients, and each has it is own merit and demerits.



REFERENCES

1. Kacerovsky M, Musilova I, Andrys C, Drahosova M, Hornychova H, Rezac A et al. (2014) Oligohydramnios in women with preterm prelabor rupture of membranes and adverse pregnancy and neonatal outcomes, *PLoSOne* **9**(8), e105882.
2. Shukla P, Bhargava M and Disha. (2014) Study of maternal and fetal outcome in preterm premature rupture of Membrane. *Journal of Evolution of Medical and Dental Sciences* **3**(7), 1789-1795.
3. Zanardo V, Vedovato S, Cosmi E, Litta P, Cavallin F, Trevisanuto D, et al. (2010) Preterm premature rupture of membranes, chorioamnion inflammatory scores and neonatal respiratory outcome, *BJOG* **117**, 94-98
4. Medina TM and Hill DA (2006) Preterm premature rupture of membranes: Diagnosis and management, *Am FamPhysician* **73**(4), 659-664.
5. Borna S, Borna H, Khazardoost S and Hantoushzadeh S. (2004) 'Perinatal outcome in preterm premature rupture of membranes with Amniotic fluid index < 5 (AFI< 5), *BMC Pregnancy Childbirth* **4**(1), 15.
6. Riyami NA, Shezawi FA, Al-Ruheli L, Al-Dughaishi T and Al-Khabori M. (2013) Perinatal outcome in pregnancies with extreme preterm premature rupture of membranes (Mid-Trimester PROM), *Sultan Qaboos Univ Med J.* **13**, 51-56.
7. Bouchghoul, H., Kayem, G., Schmitz, T. Benachi A, Sentilhes L, Dussaux C, et al. (2019) Outpatient versus inpatient care for preterm premature rupture of membranes before 34 weeks of gestation, *Sci Rep* **9**, 4280.
8. Idrisa A, Pius S and Bukar M. (2019) Maternal and neonatal outcomes in premature rupture of membranes at University of Maiduguri Teaching Hospital, Maiduguri, NorthEastern Nigeria, *Trop J ObstetGynaecol* **36**, 1520.
9. Goldenberg RL, Culhane JF, Iams JD and Romero R. (2008) Epidemiology and causes of preterm birth, *Lancet* **371**(9606), 75-84.
10. Stuart EL, Evans GS, Lin YS and Powers HJ. (2005) Reduced collagen and ascorbic acid concentrations and increased proteolytic susceptibility with prelabor fetal membrane rupture in women, *BiolReprod* **72**, 230-235.
11. Mercer BM. (2003) Preterm premature rupture of the membranes, *ObstetGynecol.* **101**(1), 178-193.
12. Okeke TC, Enwereji JO, Okoro OS, Adiri CO, Ezugwu EC, and Agu PU. (2014) The incidence and management outcome of preterm premature rupture of membranes (PPROM) in a Tertiary Hospital in Nigeria, *American Journal of Clinical Medicine Research* **2**(1), 14-17.
13. Egarter C, Leitich H, Karas H, Wieser F, Hussiein P, Kader A, et al. (1996) Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a meta analysis, *Am J ObstetGynecol.* **174**, 589-597.
14. Hocq C, Van Grambezen B, Bernard P and Debauche C. (2017) Impact of gestational age at PPRM on the short-term outcome of children born after extreme and prolonged preterm prelabor rupture of membranes in an experienced care center, *SIGNALVITAE* **13**(2), 63-70
15. Linehan, L.A., Walsh J, Morris A, Kenny L, O'Donoghue K, Dempsey E, et al. (2016) Neonatal and maternal outcomes following midtrimester preterm premature rupture of the membranes: a retrospective cohort study, *BMC Pregnancy Childbirth* **16**, 25.
16. D'souza A, Walia M, Gupta G, Samuel C, Katumalla F and Goyal S. (2017) Feto-maternal outcome in pregnancies with preterm premature rupture of membranes: a tertiary hospital experience, *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* **4**(5), 1529-1533.
17. Tavassoli F, Ghasemi M, Mohamadzade A and Sharifian J. (2010) Survey of pregnancy outcome in preterm premature rupture of membranes with amniotic fluid index < 5 and ≥ 5, *Oman Med J.* **25**(2), 118-123.
18. Elimian A, Verma U, Beneck D, Cipriano R, Visintainer P and Tejani N. (2000) Histologic chorioamnionitis, antenatal steroids and perinatal outcomes, *ObstetGynecol.* **96**, 333-336.
19. Dexter SC, Pinar H, Malee MP and Hogan J, Carpenter MW, and Vohr BR. (2000) Outcome of very low birth weight infants with histopathologic chorioamnionitis, *Obstet Gynecol.* **96**, 172-177.
20. Lieman JM, Brunfield GG, Carlo W and Ramsey PS. (2005) Preterm premature rupture of membranes: Is there an optimal gestational age for delivery?, *Obstetrics and Gynecology* **105**(1), 12-17.

