Genetic Modification of Mitochondrial DNA in Cancer Cells

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Abstract

Mitochondria is one of the most energy source in the cells, in addition to DNA encoded to several genes which relatively associated with several disease, researchers proved the role of mitochondrial in energy demand to tumor cells in addition to mitochondrial DNA role in cancer initiation and development. The present review explained different objectives related with the mitochondrial role in tumor incidence ; these included Tumor cells energy demands, Mitochondrial Mutations redundancy and allocation, Genetic disparate natural Selection in Tumor initiation, Mitochondrial Modifications Clinical Translations in Cancer, Association Mitochondria, epigenetics and Cancer and finally Injury of Mitochondria in Cancer. The present review concluded that the most important role of mitochondrial as cells an organelles for energy suppliers to tumor cells metastasis and immorality also the mutations of mtDNA and their role in carcinogenesis were well proved in different cancer types.

Key words: *mtDNA, cancer, mutation, role mtDNA, energy source.*

Introduction

Mitochondria is one of the most important organelles in the cell , the biogenesis and roles are regulated by nucleus by a stable bidirectional crosstalk, mitochondrial DNA (mtDNA) encoded 1% of mitochondrial proteins, while the others encoded by nuclear genomic including the replication and transcription proteins [1]. The mitochondrial genome in human is circular double strand consist of 16.6 kb encoded two ribosomal RNA (12S and 16S), 22 tRNA and 13 essential subunit of protein associated oxidative phosphorylation system (OXPHOS) , Other protiens involved in The electron transport chain (ETC) and the pathway of primary metabolic generating energy carrying molecule ATP which formed of five protein complexes (I-V), involving the complex II is exclusively coded via nuclear genome [2].

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The nuclear genome encoded to all proteins subunit that formed the rspitotary systems included 7 subunits of the enzyme in Com I, one subunit of the ComIII, 3 subunits of Com IV and 2 subunits of ComV. As formerly indicated, the mitochondrial proteins, included the mtDNA processing like transcription and translation proteins and replication, encoded by the nuclear genes and are subjected to the mitochondrion by particular transport systems, about 2000 small non-coding RNAs (mitosRNAs) were detected, that have role the natural mitochondrial gene expression control, showed an underestimated scale of mitochondrial functional complexity [3].

Otherwise, the investigations deal with antisense anti-termination tRNAs and delRNAs focus a de nova facts on incoming processing extending the coding prospect of mitochondrial genome [4, 5]. The ETC byproducts of the steadily create reactive oxygen species (ROS) which may seriously harm the mitDNA that cusses different types of mutation and the these lesions accumulation in the mtDNA molecules result in subsequent the dysfunction in mitochondria , like number changes, morphology and functioning, as

noticed in tumor cells [6].

The mitochondrial DNA is more exposed to mutated than nuclear DNA, because of the absence specific proteins like histones and the loss of structure chromatin, rarity of introns, also the less effective recover mechanisms of mtDNA and a direct exposed to the damaging ROS created pending ATP generation within the mitochondria [7].

In spite of low scales of ROS to organize the signaling in the cells and are substantial for normal endurance and reproduction of cells , thumbing ROS generation is repeatedly noticed in neoplastic cells. The theory of mitochondrial free radical of aging the cumulating of harmful mtDNA mutations, inhibition of oxidative phosphorylation, furthermore the disturbance in antioxidant enzymes expression leads to exponential overproduction of reactive oxygen species, This evaded situation consist □vicious cycle□ which is the fundamental of a broad extent of pathologies, phrased as □free radical diseases□ like tumor, atherosclerosis, neurodegeneration, chronic inflammation and diabetes mellitus [8].

Substantially, alongside the apparent creation of oxidative nucleotide deterioration to the mtDNA, the free radicals triggered cancers by different ways, involving settlement of hypoxia inducible factor (HIF)-α, raised the flux of calcium, inhibition of key phosphatases [9–11].

Tumor cells energy demands

Formidable proof now proposes that the energy demands of fast reproducing tumor cells and primary cells are supported by the glycolytic metabolism and the cell differentiation with high energy requested maximize the utilization of mitochondrial respiration [12]. Additionally, the irregular division of stem cells and cancer stem cells have high reproductive potency preferentially utilize glycolysis [13].

Nonetheless, several cancer cell lines possess so high respiration averages, and raising proof supposes a convoluted relation between the energy metabolism of tumor cells with the tumor formation and progression [12–15].

The Motivating metastatic tumor cells without mtDNA (r0 cells) cannot used their mitochondria for respiration develop in culture medium affixed with pyruvate and uridine, though their development is usually extremely slower than the growth of parental cells. These cells display raised cell surface oxygen consuming through their plasma membrane electron transport, a compensative passageway intellect to correct for the setting up of intracellular reductants in respiration obscurity [16], an agent that requires to be taken into consideration in estimating glycolysis participation to total energy metabolism.

Mitochondrial Mutations redundancy and allocation

The difficulty in mutation detection of cancer mtDNA related to small differences linked with the organelles genome. Most significantly, the vicinity of ROS created through normal metabolic events elevated the danger of mtDNA disturbance and insecurity [17].

The impact of ROS in the modifications of mtDNA is upheld via common raise in somewhat cancers of transitions at purines [18]. this deterioration, associated with low repair mechanisms comparative to the genome of nucleus , cause an mtDNA mutation range greater than the nuclear genome [19].

Empirical proof supposes that the operation of endogenous mutational are more effect in the range of mtDNA mutation, as dissenting to the exogenous carcinogens such as environment chemicals and UV light [20]. Two additional features are pertinent to explicate the mtDNA disparate redundancy and allocate.

At first, in the cell the mitochondria and their genomes are found in high copy nombers hundreds or thousands. Secondly, the mtDNA is matrilineal heredity in humans, thus there was single mtDNA haplotype but it shows Heteroplasmy pattern due to the impacts of numerous copies). The mutation of germline mtDNA was inherited from mother and are constituently existed over the offspring. Moreover The Germline mtDNA disparate are valuable for defining individuals to particular haplogroups [21], that able to thereafter be correlated to ancestral matrilineal relations [22].

The haplogrouping can be utilized in relations characteristic among individuals and populations, several haplogroups consist of sequences pattern may be found participates to cancer tendency [23–24]. some mutation

in somatic cell manifest haplogroup transmutation [25], some types of mutation in mtDNA reflect specific pattern in cancer cells.

Many cancer mutation [20, 26] observed specific pattern of mutation landscape in mtDNA related to tumor. Though this latter tendency different to presented in the nuclear DNA, it does make germline patterns shaping primate mutation of mtDNA , mtDNA of human in general includes mutation hotspots in both rRNA and genes coding for protein synthesis, expressing synonymous, non-synonymous, and non-expressed sites, with minimal changes in tRNAs [27]. Whole-genome analysis of somatic mutations related to cancer reflects this relative frequency of mutation in divers kinds of sequence [28, 29].

The mutation in nuclear and mitochondrial DNA of cancer types are observed as heterogeneous [20, 26]. Morever, the somatic mutations relative rate varying in individual cases was 13 - 63% according to types of cancer and disparate the mtDNA may be found throughout cancer types or exist only in single kind of tumor [30, 31].

Lee et al, reviewed a differences between allocate and kinds of somatic mtDNA mutations [32]; they clarified express the patterns arising as pertinent throughout tumor kinds. Some genes of mitochondrial have reported somatic mutations that may engaged in tumor initiation. Somatic mtDNA changes throughout cancer types, are riches with non-synonymous disparate compared to synonymous disparate [29, 30].

The mtDNA genes coding proteins related to the different complexes of the mitochondrial respiratory chain. The Com I called NADH dehydrogenase is encoded by 7 mtDNA genes (*ND1-6*, including *ND4L*), its most repeatedly includes disparate correlated to tumorigenesis (33). Like *ND5* is hardened for somatic mutations [28, 30, 34], that may modify development of tumor [35].

The Complex III, only *CYTB* gene is encoded by mtDNA, includes lower authenticated somatic disparate. the bladder cancer is exception , where this complex is importantly more affected than the others [36] and deletion seven amino acid observed in populations that linked with bladder tumor progression in experimental work [37, 38]. The Com. IV cytochrome c oxidase have 3 genes expressed in mitochondria (*COX1-3*), researchers found that the mutations in *COX1* that linked to colorectal tumor may decrease expression or reduce the respiratory chain effects [39].

The Com V or ATP synthase consist of double genes located on mitochondrial DNA (*ATP6* and *ATP8*). The *ATP6* gene observed to possess more predisposition to mutation than *ATP8* in breast cancer patient , which may exhibits alterations in energy metabolism among tumor cells [40]. Throughout genes coding proteins, modifications to Complexes I and IV found to be the most effective in stimulating tumor initiation [41].

The genome of mitochondria involves 22 tRNAs, constituting small ratio attribution of the nucleotide sequence. The Somatic mutations in tRNA are not redundantly authenticated in correlation to tumor in human, in spite of they are generally engaged in a various other defect in primary respiratory chain [42]. As a result of low ration in tRNA mutations that correlated with tumor, they symbolize to show changes to secondary structures [26] also the disparate may lead to instability and modified mitochondrial labor [28].

In similar manner, the two rRNA genes mutated expressed via mitochondria have high relatively harmful impacts than alterations to genes coding protein [42]; though, alterations to the rRNA were low happened. While the genic sites of the mitochondrial DNA are a sensible goal for appreciating tumor mutations, hyper changeable (HV) regions in the non-expressed mtDNA also express common mutational hotspots. the somatic and germline mutations in the mtDNA happened preferentially in two sites of this site, HV1 and HV2 [43].

The cancer Researches interested massively on the genetic disparate in D loop , its long segment of control region. Also the non-coding region observed in several animal mtDNAs and is formed by insertion third linear strand DNA, Given the linkage between control region and the mitochondrial molecular processing, the D-loop mutation can effect in mitochondrial copy number and organization [44].

In cancer the mutation in D-loop are well-studied to all mtDNA cancer disparate. This site has large alterations rang to appreciate cell lineages progression

and reproduction [45]. In cancer the D-loop Mutations are also more exist [46], and large scale of somatic D-loop mutations linked to poor prognosis in breast cancer [47].

In spite of possible engagements of D-loop mutations in function of mitochondria in cancer, it is unclear whether these disparate are a causal or simply correlated phenomenon [45, 47, 48].

Genetic disparate natural Selection in Tumor initiation

The theory of cancer initiation is focused on the genetic disorder inn some genes called [49]. Later accumulation of mutation in the genome as a consequence of these disparate in oncogenes, resulted to scan of features identifying tumor progression [50].

The theory of somatic mutation, is hard to reconcile to authenticated mtDNA disparate linked to tumor [51]. Raising proof engaging the tumor risk of mitochondria, initiation, and development contributed to a growing information's of cancer as a mitochondrial metabolic disease. This phenomena constructed from different suggestions including the natural selection, heteroplasmy, and the combined impacts of genetic modifications throughout the DNA. After the initiation mitochondrial mutations, disparate are subsequently submitted to various molecular, cellular, and population level operations [52].

The carcinogenic intuition via evolutionary operations, the mutations in the genome initiate , then submitted to the natural selection and/or genetic divergence. The impacts of choosing are commonly separated into two groups in tumor investigation: 1st clarifying the negative selection, mean that the harmful alleles are deleted from the population, 2ed the positive selection, mean the beneficial alleles raise in redundancy in the population (may be toward fixation). the mutations may be neutral and not pass to selective forces but stayed reproduce stochastically by drift. Many datasets and applications have been applied to screen for mtDNA mutations selection linked with cancer. In human history, the germline mtDNA mutations consider as a negative selection [53].

According to large samples number of mtDNA suggested that the mutations are submitted to same selective features, in any case of the initiate in normal or cancer cells [54].The harmful mutations head to be choose against [55]. in some healthy tissues alternately express positive selection on mtDNA somatic mutations. a positive selection in liver eliminated mitochondrial labor to reduce damage ensuing from byproducts of metabolism [56].

The mutations selection associated to cancer initiation, reflected of somatic mtDNA mutations through oncocytic cancer types reflects that disparate linked with cancer are indiscernible from random [57]. Meanwhile , a linkage has been found between the number of somatic mtDNA mutations and the patients endurance in breast cancer, with proof for both positive and deliberated negative selection for somatic missense mutations [28].

The mtDNA Scanning studies using metastases in bone represented statistically high variation than metastases in soft tissue and primary [58]. These studies, though apparently paradoxically, accumulatively focus the light on two points in the impact on mtDNA mutations in cancer: the 1st one, the time grade and discrimination of somatic from germline mutations matters, and 2ed ,the manners of selection

Mitochondrial Modifications Clinical Translations in Cancer

While the association between the mutation in germline mtDNA and cancer hazard is well discussed overhead (section Mitochondrial Mutations redundancy and allocate), also studies found that mtDNA disparate can apprize cancer disclosure, curing, and prognosis. Due to the presence of mitochondria in large copy number within the cells and are clonal by nature, the have capability to assist in disclosure and detection of some cancer kinds [59].

The usage of mtDNA as a genetic marker not bordered to cancer, yet, as mtDNA disparate correlated to tumor also can be revealed in lower invasive bodily fluids [60], like the usage of urine to diagnosis the cancer in bladder [36]. Also involve the utilization of serum and aspirate fluids for colorectal and breast cancer, diagnosis respectively [61, 62].

Multiple researchers have observed the interest of

mitochondria utilization to cure the cancer [17, 63, 64, 65–67], even declaring that "comprehension the mechanisms of mitochondrial labor throughout tumorgenesis will be crucial for the next descent of cancer remedies" [68]. According to apoptosis is a major participator in lowering tumor cells in addition to cell death restraint is mitochondrial organized , it logically pursues that the mutations in mtDNA may modify restrains to cancer remedy [69].

Actually, the case study observed that the mutation in *ND4* in ovarian cancer may be causes resistance to chemotherapy [70] also mutations in D-loop have been found that related to chemo resistance in patients with colorectal cancer [71]. Finally the reduction in mtDNA components is related with prognosis enhancement in breast cancer patients subjected to anthracycline-based chemotherapy [72].

Absolutely, the contrast stand claims for mtDNA gene expression and mutations have confined clinical features, as in ovarian cancer [73]. The association of individualized metabolic operations with myriad diversity in the mtDNA genome and nuclear persuades more work into the used of personalized medicine in curing cancer [74].

Association Mitochondria, epigenetics and Cancer

The modern cancer researches focused on the mitoepigenetics that mean the epigenetic organization like alterations of mtDNA gene expression and the symmetric interactions with the nuclear genome [75]. The variation in mitochondrial methylation was observed among natural human tissues [76]. Furthermore, allover-genome methylation is correlated with various human diseases, of which the cancer disease [77]. These basic features resulted to an expectation that mtDNA epigenetic assortments able to enhance development of tumor. The impact of mitochondrial give a global manners of gene expression [78] adds credence to a possible linkage between mtDNA copy number and methylation [75]. Furthermore, a study observed a mechanism for this association a mitochondrial disrupt checkpoint may stimulate to remedy injured mitochondria, the mitocheckpoint could prospect change epi-genetic manners and genomic stability when the signaling happens between the nucleus and mitochondria, [79].

These proofs accumulatively suppose the relation of mtDNA epigenetics to cancer, have several benefit formerly evidenced the usage of mtDNA methylation as a biomarker for diagnostic objectives [75,80]. Yet, potential relations and implementation have yet to be quite explored, particularly when we have shortage in the methylation quantity throughout tumor kinds and stages [81]. Filling these hiatus in acknowledgement may help in bearing down preceding discordant proof among cancer kinds.

Injury of Mitochondria in Cancer

In spite of mitochondrial injury was assumed by Warburg to be an occasion of tumors and this judgment is remain boosted by several investigations, massive proof directs to complexes nuclear genetic modification, some of the mitochondrial labor, being the main cause of cancer with environmentally commanded epigenetic alterations participating in methods that still to be completely understood.

The mtDNA modification happen in most tumors because of the elevation mutation ratio compared with DNA in nuclear and indigent repair mechanics, the involvement mtDNA mutation in the cancer progression has been resides in only a plain number of cancers [82–84]. Another injury in mitochondria due to the oxidative deterioration generated from sustained inefficient respiration and oxygen radical creation, not directly correlated to genome injury may also happen, but how this deterioration plays out in terms of cancer formation and development is still unclear.

Though, the little alterations that participate to rebalancing the energy metabolism toward glycolysis may do a role in tumor inception and development. Many articles authenticate a function of mtDNA mutations in formation of cancer and metastasis. As example, HeLar0 cells which do not form tumors after xenotransplantation were altered into malignant cells able of carcinoma inception by informing mtDNA with particular mutations [85].

The mtDNA mutation was also presented to be significant for the these cell metastatic tendency [86]. Interestingly, Ishikawa and colleagues reciprocated around the mtDNA between metastatic and non-metastatic cells in breast cancer, after which the original

non metastatic cells initiated metastatic tumors and vice versa [87]. This robustly refers that several mutations in mtDNA, in addition to nuclear mutations, can be significant for metastasis.

Conclusion

The present review focused on the association between genius of mtDNA mutations and tumor throughout numerous cancer types. Some Common manner of mutation are explanation by evolutionary operations impacting the existence of these mutations, supplying a significant basis for mtDNA and cancer studies.

Present study recommended using best practices in estimating mtDNA modifications linked with tumor and suppose promising fields for a new research. Modifications to mitochondrial dynamics through tumorigenesis manage the total gamut of possibilities, metabolism, impacting biogenesis and virtually all other quarters of mitochondrial role.

to data concerning the somatic mutation in mtDNA correlated with tumor cumulate, it is clear that modification in the mtDNA contributed in tumorigenesis trigger while others simple fund with cancer develops. Mutations in nuclear-encoded genes, along with corresponding alterations to the cellular labor of ambient cells, could enhance additional mtDNA modifications or applies qualification to what alterations may reproduce.

Defining particular mutations valuable as genetic marker, for this reason, will crave wider sampling of mitochondrial genomes from varied tumor kinds at numerous phases of development, and cautious resolving to estimate the redundancy to mutation in tumor. Mitochondria related with normal and cancer cells show a microscopic tale of two cities. Mutation observed in each genomes, but different were be observed of cellular and molecular powers in the destiny of such disparate. This duality applies the chance to mark both basic acknowledgement of cellular labor and translational medicine.

Conflict of Interest: Nil

Source of Funding: Self

Ethical Clearance: Nil for review article.

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Influence of Melatonin in the treatment of experimental Enterobius vermicularis infection

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Abstract

This study aims to realization the conceivable therapeutic of melatonin effects experimental against *Enterobius vermicularis* in rats. Implement this experiment during the period from August 2019 to January 2020. *E.vermicularis* infected with male wistar rats orally with dose 15mg/kg melatonin former of body weight for 30 day showed significantly reduction in the number of eggs and worms compared with rats orally with dose 15mg/kg melatonin accompanying and untreated rats for 30 day ($P < 0.05$).Histologically in intestine examined show increase numbers of leucocytes produce, necrosis significant scatter and reduction this parasite of tissue in rats treated with melatonin. This results show influence of melatonin in the control on *Enterobiosis* and suggestion that this drug usefulness in *Enterobius vermicularis* infection therapy.

Keyword: *Eggs, Worms, Enterobius vermicularis, Melatonin, Former.*

Introduction

Enterobius vermicularis is helminthes more common human parasitic Nematoda infected the bowel but the children worldwide may reach to 40 million infestations in USA and Europe especially school students [(1).] Infection may be associated with poor hygiene or behavioral environments in family overcrowded and orphanages where transfer the eggs pinworm from person to another by finger polluted or via anus into mouth directly may transmit by eat contaminated food indirectly [(2).] The clinical symptoms occurs because the migration of the gravid female worst at night when lays eggs lead to excitement, lack sleep, appetite and weight decrease , vomiting and abdominal pain [(3).]

There are many drugs can be help in eliminated on pinworm else will not be beneficial, most common drug is mebendazole family these killed the adult worms only addition to increased resistance these drugs wherefore need for the development of new methods for control and enucleate of the parasitic disease [(4).]

Recently studies suggests that melatonin immune enhance function through presence of melatonin receptor in immune organs, Melatonin is biological processes recurring naturally hormone synthesized in most the pineal gland to blood of mammals also is synthesis in deferent cells, tissues and organs like lymphocytes, skin, eyes and gastrointestinal duct [(5).] Melatonin has been examination studies in parasitic, virus and bacterial infestations [(6).] Act the melatonin to promote antigen display, phagocytic activities and production of monocytes [(7).] Melatonin have important immune-modulatory effects e.g. *Plasmodium* that hepatocytes colonies and red blood cells will causes in death of malaria through that melatonin have precursors derived from the tryptophan will calcium release and modulate the cell cycle of *P. falciparum* [(8).] The melatonin treatment with *Schistosoma mansoni* act on decrease oxidative injury and increase permanence of hamster infected [(9).]

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The goal of this study to specify influenceof melatonin drug against *Enterobius vermicularis* by examined in rats.

Materials And Methods

Collection eggs of *Enterobius vermicularis*:

Eggs were collected from infected children of school in Al-Najaf city, gathered in anus they suffer from anal itching by transparent adhesive tape [10], these eggs incubation at 36ºC in wet flask for 5 days, most eggs were ivied released through vexation of the body, these eggs contained within larva notice circulation movement after three from incubated inside shell, some of them hatch naturally as expressed [11] kept unit used in the experiment.

Preparation of Melatonin Solution

Consider melatonin slightly soluble in water so used dimethyl sulfide and ethanol (DMSO/Germany) to dissolve. Take 2 mg / milliliter 99.9 DMSO-melatonin were prepared as stock solution [12].

Preparation and Infection Animals

90 male wistar rats were weight 100-110 g kept under light period 12h light and 12h dark where divided into three groups each group contain 30 rats were placed in plastic cages contain food and water with a floor furnished with sawdust, good ventilation and continuous cleaning of the cages,500 eggs number within movement larva examined under microscopic were counted from eggs sedimentation by slide chamber, group one were 30 rats infected with 500 egg of *E.vermicularis* only orally as control without drug, group two (Former) were 30 rats were inoculated melatonin pretreated for 7 days before the infection daily orally at dose of 15 mg / kg body weight where dissolved in distilled water then give oral 500 eggs for 30 day and group three (Accompanying) inoculated melatonin with eggs daily at dose of 15 mg / kg body weight give oral 500 eggs for 30 days. Three groups were examining the stool after 10, 20 and 30 days of infection by microscope.

Histology Animals

Rats were numbness with 2.5 pentobarbital and postmortem, intestine were reapers then inglorious 10 formaldehyde to make a histological section of the infection and treated, eosin-haematoxylin stain then examined by microscope in magnification of 100x [13].

Statistical Analysis

Results were calculated by analyses data the one way by ANOVA test and statistical significance between groups analyses when ($P < 0.05$).

Results

As shown in table (1) , there is a significant reduce in *E.vermicularis* infection in rats treated with melatonin former at the dose of 15 mg/kg which were 1 and 0 for eggs and worms respectively, while there is a significant decrease in *E. vermicularis* infection in rats treated with melatonin accompanying at a dose of 15 mg/kg which were 21 and 10 for eggs and worms respectively, both after 30 day of treatment compared with control without treated were 390 and 495 for eggs and worms respectively after 30 day of infection. This may due to protective effect of melatonin is put off the appearance of disease, retard death and reduce the mortality rate.

Table 1: Influence of Melatonin drug on count of Eggs & Worms of *Enterobius vermicularis* in rats per 20 microscope fields / days.

Dose Mg/kg	10days		20days		30days		F P value
	Eggs	Worms	Eggs	Worms	Eggs	Worms	
Control (+ve)	500	473	470	480	390	495	58.26
Melatonin Former 15 mg/kg	213	92	45	9	1	0	0.001
Melatonin Accompanying 15 mg/kg	322	211	105	57	21	10	(LSD = 32)

LSD : Least Significant Difference

Discussion

Enterobiosis is a human intestinal parasitic disease caused by pinworm infects a lot of people especially children causes symptoms e.g. anal itching, painful or difficult urination, irritation, insomnia repeated infection causes weakened immunity and may lead to death in the absence of treatment [14]. Because of resistance to conventional drug and repeated infection, must search for alternative drugs and low toxicity [15]. In the present study used melatonin drug is suggested that can therapeutic differ agent like immune enhance functions, antioxidant effect, bacterial, fungi viral, and parasites infections, shown significant reduce *E.vermicularis* with melatonin former when dose 15 mg/kg were 1 and 0 for eggs and worms respectively while significant decrease *E.vermicularis* with melatonin accompanying when dose 15 mg/kg were 21 and 10 for eggs and worms respectively, both after 30 day of treatment compared with control without treated were 390 and 495 for eggs and worms respectively after 30 day of infection, this indicates that give melatonin former enhances of the immune response, as in Table 1 .

This may due to protective effect of melatonin is put off the appearance of disease, retard death and reduce the mortality rate [16] , these study consistent with [17] that melatonin have control through of experimental the *Trypanosoma cruzi* infection and lead to reduce the parasitemia levels in rats. Another reported by [18] that melatonin drug cellular immunity activity by increased production lymphocyte in *Toxoplasma gondii* infected in rats. As in other study show reduce *Leishmania* infection to 40 in hamsters infected during the when serum melatonin being high compare to animals infected when melatonin level being low, this indicates that melatonin receptors plays an important role in leishmaniases treatment [19].

As shown in the current study, it have been seen in histological analysis for untreated section granuloma fashioning in the intestine, necrosis, adenoma and hemorrhage of the bowel [20].

There was a statistically increased numbers of leucocytes production which observed in both the accompanying and former melatonin treatment observation tissues necrosis scatter among regions and inflammatory cells sneak shrill comparison with *E.vermicularis* infection only ($P < 0.05$) may due to melatonin increased immune-modulatory activates and have ability on stimulate innate immune cells in positive attachment between melatonin and phagocytic efficacy with infected [21] .

This study agreed with [22] showed that exogenously manage melatonin significant reduced the amoebic necrosis areas also increased of leukophagocytosis and number of the dead amoebae.

In other study *Trypanosoma brucei* parasite was given the melatonin infected rats make histological changes in pineal gland where caused in reduce plasma level which may due to release of inflammatory mediators and become not inroad cell [23].

Ethical Clearance : Taken from University of Kufa ethical committee

Source of Funding : Self

Conflict of Interest : Nil

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Dynamic Changes in Salivary Cortisol and Protein among Dental Students

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Abstract

Background: Student assessments are the traditional methods of assessing academic success, and they are considered to affect one's career. This study evaluated the levels of salivary stress biomarkers represented by cortisol and total salivary protein during final academic assessments of dental undergraduates.

Methods: Saliva samples were obtained, one before the exam another afterwards. Concentrations of salivary stress biomarkers were obtained by enzyme-linked immunosorbent assay (ELISA).

Results: Before the exam, the two parameters were dramatically higher than afterwards, with a substantial difference between the levels of salivary protein and cortisol (p=0.000, 0.000 consecutively).

Conclusion: Stress induced by academic examinations may increase the level of salivary stress biomarkers in the short term.

Keywords: *Academic stress; cortisol; ELISA; saliva; salivary stress biomarkers*

Introduction

Academic exams are considered to be among the most challenging experiences for students, since passing or failing typically has implications for career development[1]. In particular, two primary systems or locations in the brain are involved in the stress response: the sympatho-adrenomedullary and system hypothalamus-pituitary-adrenocortical axis[1]. Increased secretion of cortisol in the adrenal cortex occurs due to the activation of HPA. Therefore, salivary cortisol represents the activity of HPA and is a more effective assessment than blood collection in stress research, which can induce spurious increases in cortisol secretion, representing the hyper-stress component[1]. A wide range of data has revealed that several kinds of psychological stress can result in HPA activation, leading to cortisol release and subsequently significantly higher salivary cortisol levels than resting baseline levels. The principal glucocorticoid in the human adrenal cortex is cortisol, which is synthesised from cholesterol. Higher levels of cortisol as a response to biochemical stress contribute to the well-characterised suppression of HPA related to health events and cognition[1]. Salivary cortisol is present in a stable, unbound form and is the only fraction of hormones that display metabolic activity in combination with unbound plasma cortisol in the blood. Unbound cortisol reaches cells through passive diffusion due to lower of molecular weight and lipophilic nature, making it is possible to measure free cortisol in many body fluids. Up to 95% of secreted cortisol attaches to large protein molecules, like albumin and it is transported in the blood in the body. Salivary proteins have important functions, including the health of the oral cavity; the nutrition, survival and colonisation of microorganisms; and the adhesion and aggregation of microorganisms. Moreover, greater concentrations of total protein in response to stress lead to changes in saliva chemical properties, including oral surface adhesion or lubrication,

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and viscosity. Stress levels vary in different areas of education and learning, and higher stress levels could undermine the cognitive functions and learning abilities of students[1]. Moreover, the prevalence of depression, anxiety and psychological distress among medical students is increasing[1]. To investigate this phenomenon, this study used salivary cortisol as a biomarker for stress assessment during academic examinations, with higher levels found prior to a written test and its anticipation. Many studies have reported a rise in stress hormones (levels of cortisol) in anticipation of stressful experiences, such as oral exams, cardiac surgery and dental-treatment[2]. Moreover, the response to physical or psychological stress in the body increases the cortisol secretion. Stress can be beneficial, of course, as it can boost drive and energy to get through stressful situations, such as examinations and work deadlines[3,4]. Students face numerous academic problems in today's highly competitive world, however, including exam stress, lack of interest in a class and failure to understand a subject[5]. Exam stress is the feeling of fear or anxiety over one's performance in examinations[6], and academic stress can increase students' anxiety levels[7]. Interest has been rising in identifying and using biomarkers in saliva as a more evaluative way to measure stress. The investigation of stress biomarkers has achieved recognition because saliva sample collection is standardised, non-invasive and easy to manage. Studies have shown that saliva can be used in chair-side tests for many oral and systemic diseases[8]. Saliva is useful because of its many analytes that are affected by a variety of conditions and physiological and pathological stressors[9]. Therefore, this study was designed to confirm salivary cortisol and total protein levels during psychological stress[9] among undergraduate students in a dental college.

Materials and methods

From 2016–2017, a cross-sectional study has been conducted at the College of Dentistry, University of Anbar, Iraq. A total of 12 undergraduate students (6 males and 6 females) aged 21–23 years were randomly selected and recruited from different academic years to study. The study's objective and protocol were explained to all the recruited students, and their voluntary consent was obtained prior to participation. Two unstimulated saliva samples were collected from each student. In order to decrease the presence of food debris and consequent salivation stimulation, students were asked not to eat and drink water only about an hour prior to sample collection. The first sample was taken 30 minutes before a written examination at 8:30 am, and the second sample was taken at 12:00 pm after the examination was complete. Each student was instructed to rinse his or her mouth to remove debris. De-ionised water was used to rinse the mouth, and the participants were then asked to spit for 5 minutes in a special sampling container. The container was labelled with a collection number (1 or 2), date and time. All salivary samples were centrifuged at 3,000 rpm for 10 min to isolate pure saliva. Total protein and cortisol concentrations were calculated using a special kit (SPINREACT, Spain) with an enzyme-linked immunosorbent assay, as directed by the manufacturer.

Statistical Analyses

The data analysis was performed using version 11.0 of SPSS. A *p*-value smaller than 0.05 was determined as statistically significant. To check for discrepancies in the categorical variables, a Chi-square test was used.

Results

A total of 12 dental students (6 male, 6 female) from different academic years were recruited for this research to measure their levels of total free salivary cortisol (ng/ml) and total protein content in saliva. As shown in Figures 1 and 2, both parameters were significantly higher before the exam than afterwards, with a substantial difference between salivary protein and cortisol levels (p=0.000, 0.000 consecutively).

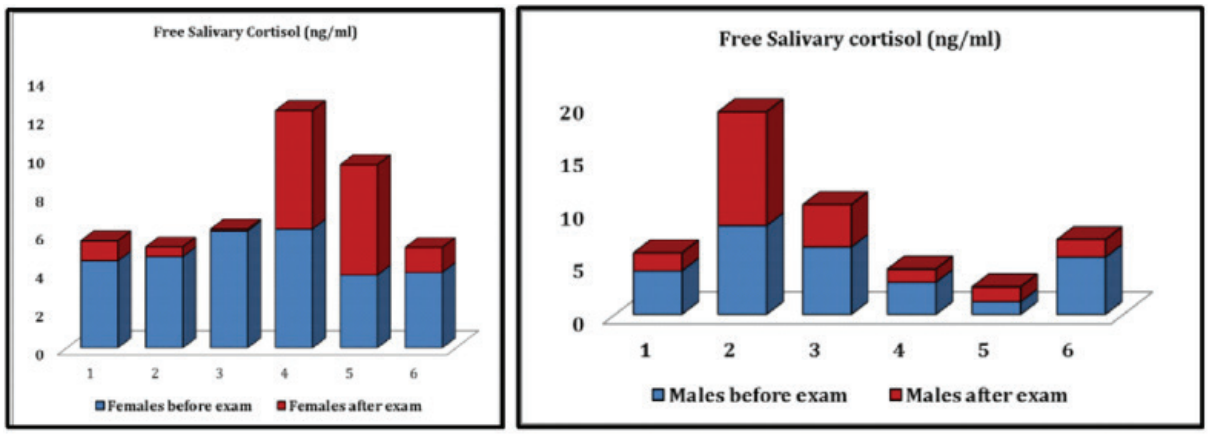

Figure 1: Levels of total free salivary cortisol (ng/ml) before and after the exam.

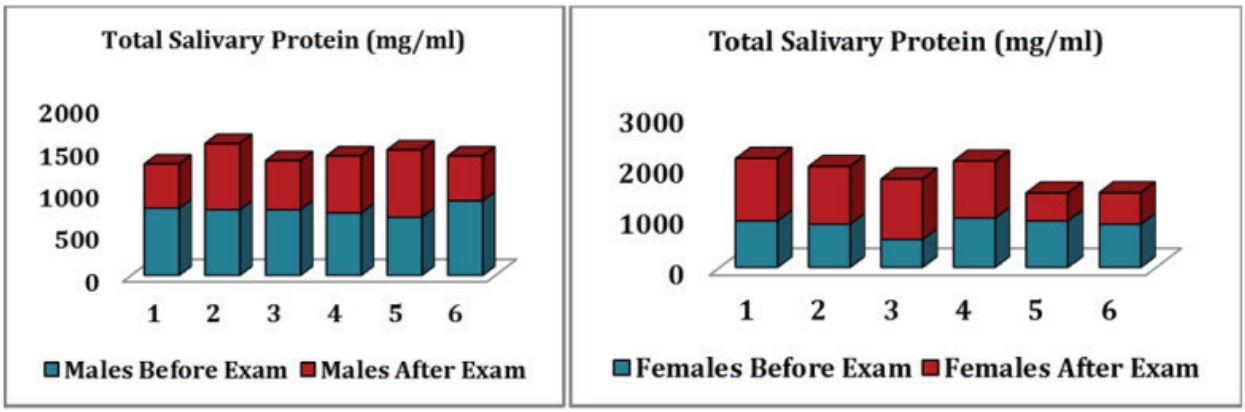

Figure 2: Levels of total free salivary protein (mg/ml) before and after the exam.

Discussion

Saliva plays an important role in the maintenance of oral hygiene. Various studies have shown that salivation changes often occur due to stress. In this study, we correlated the levels of certain parameters in saliva with the stress induced by an examination in medical students. Protein levels in saliva were significantly higher before the examination than afterwards, a finding consistent with that of Nauvoma et al., who also showed a significant increase in protein concentrations in saliva immediately after stress exposure[10]. Another study by Al-Nuaimy et al. showed similar findings by estimating protein concentrations before an oral academic exam and after one month of holiday break[11]. To understand the mechanism behind this increased protein concentration, the activation of salivary glands as a sympathetic intervention during exposure to stress to control protein secretion has also been explored[10, 12]. The autonomic nervous system primarily controls protein secretion mainly by three salivary glands: parotid, sublingual and submandibular. The release of protein from the submandibular glands and parotid is elicited by stimulating the sympathetic system, and protein release from the sublingual gland is usually elicited by stimulating the parasympathetic system[13].

We also measured free salivary cortisol levels during a stress condition before and after the academic exam. During chronic stress, alteration in cortisol levels is prominent. Cortisol is a stress hormone that is synthesised in the cortex of the adrenal gland[14]. As discussed earlier, the measurement of cortisol in saliva is superior to that in serum because a salivary assay enables the measurement of unbound cortisol.

We observed significantly higher cortisol levels in saliva before the academic examination in both males and females than afterwards, showing a direct correlation between saliva cortisol levels and stress.

Other studies have reported similar findings, indicating that training during medical courses causes higher incidences of psychological stress in students and that academic examinations are major stressors for students, likely because their performance affects their future careers[2,15]. This increased stress leads to increased levels of cortisol[10,11,16]. The increase in cortisol levels is attributed to HPA axis activity, which is more intense during stress reactions. Hypothalamus-level stressors activate the secretion of CRH and AVP, which stimulate the frontal lobe of the pituitary gland to release adenocorticotroic hormone (ACTH). ACTH stimulates the synthesis of cortisol and its secretion in the adrenal cells. Stress reactions are exhaustive and damaging to the body; indeed, cortisol limits and minimises the catabolic and immunosuppressive effects of stress reactions through a negative feedback mechanism[17,18].

This study therefore demonstrates that the stress of academic examination affected important components of saliva, including protein and cortisol, which decreased after the exam was over. This suggests that these levels are a short-term response to stress.

Conclusion

This study has shown increased protein and cortisol concentrations in saliva before the commencement of an academic exam, which decreased after the exam was over, suggesting that stress precipitates short-term changes in saliva composition. Higher levels of cortisol during an examination can reduce stress during the examination.

Conflict of Interest: All the authors declare no conflicts of interest.

Funding: N/A

Acknowledgement: We thank our dental colleagues at the College of Dentistry, University of Anbar, who aided the investigation.

Ethical Approval: The study was conducted in compliance with the Helsinki Declaration and with the approval of the Regional Committee on Ethics, which is represented by the Medical Ethics Committee of the Ministry of Health in Iraq.

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Prevalence of Smoking among Iraqi Female Medical Providers in Baghdad

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Abstract

Background: Cigarette smoking is the largest preventable risk factor for morbidity and mortality in developed countries. Healthcare providers who smoke are less likely to advise patients to quit smoking. Being a female and smoker adding more burdens on society.

The obkecibe o the studu is to assess the prevalence of smoking among Iraqi female medical provider.A descriptive cross-sectional study with an analytic element. Data collection was done via electronic questionnaire forms distributed online to contact list for 450 -easy to reach- female health providers (doctors, dentists, pharmacists) who work in different hospitals, PHCs and health institutes in Iraq.Nearly 15.3% of the samples were smokers, 53% of sample was 20-29 years while nearly 62% of sample was married. About two third of sample had bachelor degree (66.2) while nearly half of the sample (52.9) were doctors. Regarding the place of work about (55.6) of sample were working in hospital and the years of service were equally distributed between <5 years and >5 years. Nearly half of the sample has husbands or friends who are smokers. The smoking environment was significantly affecting the smoking status while there is no association between age, marital status, education, field of work, place of work and years of service.The percentage of female smokers among medical service providers is high, and female doctors got the highest rate. With regard to age, the age group between 20-29 was the highest among female smokers. The results also showed a higher percentage among those who work in hospitals, and the largest proportion of female smokers was among those who had spouses or friends who smoked**.**

Keywords: *smoking, Iraqi female, medical provider*

Introduction

Worldwide, tobacco use represents one of the major causes of death and the main preventable cause of lifestyle-related diseases, such as lung cancer, chronic obstructive pulmonary disease, and coronary heart disease [(1)]. Smoking is a major preventable cause of morbidity and mortality [(2)]. Smoking for anyone, at any age, is dangerous and can lead to preventable disease, and even death. But, for women, smoking carries certain additional risks [(3)]. About 250 million women in the world are daily smokers. About 22 percent of women in developed countries and 9 percent of women in developing countries smoke tobacco. In addition, many women in south Asia chew tobacco[(4)].The tobacco industry promotes cigarettes to women using seductive but false images of vitality, slimness, modernity, emancipation, sophistication, and sexual allure. In reality, it causes disease and death. Tobacco companies have now produced a range of brands aimed at women. Most notable are the "women only" brands: these "feminized" cigarettes are long, extra-slim, low-tar, light-colored or menthol [(4)]. Health care professionals play a prominent role in promoting tobacco control and smoking cessation programs. However, their smoking habits may prevent them from providing unbiased advice on smoking cessation and may even prevent them from being efficiently involved in cessation programs designed for patients [(5)]. Physicians who smoke are less likely to advise patients to quit smoking. Also, it is less expected from them to assess patient's will to refrain from smoking [(6)]. This research throws a light on

smoking among female medical providers in Iraq, and aims to estimate its prevalence.

It is vital to assess health professionals' smoking habits for two reasons. First, they have a direct effect on their health and wellbeing. Secondly, it has been shown that physicians who smoke tobacco are less likely to advise their patients regarding the health hazards of tobacco smoking [7].

Methods

A descriptive cross-sectional study with an analytic element. Data collection was done via electronic questionnaire forms distributed online to contact list for 450 -easy to reach- female health providers (doctors, dentists, pharmacists) who work in different hospitals, PHCs and health institutes in Iraq. The questionnaire included sociodemographic & occupational information's of participants: age, marital status, no. of children, education, field of work, place of work, and years of service. Collected data were fed, statistically analyzed, presented using SPSS V.20.

Results

The distribution of the sample by sociodemographic variables is presented in table 1: About 53% of sample was 20-29 years old while nearly 62% of sample was married with nearly (69.1%) of the sample had number of children between (0-2) . About two thirds of sample had bachelor degree (66.2%), while nearly half of the sample (52.9%) was doctors. Regarding the place of work (55.6) of sample were working in hospital and years of service were equally distributed between <5 years and >5 years. According to table 2: (15.3%) of the sample was smokers. Nearly half the sample has smoking husbands or friends. The smoking environment was significantly affecting the smoking status, while according to table 3 there is no statistical association between smoking with age, marital status, number of children, education, field of work, place of work or years of service.

Nearly half (53.6%) smokers reported enjoyment as the main reason for smoking, while non-smoking reasons for the majority (64.6%) were fear from health risks (table 4).

Vast majority of smokers (72.4%) were smoking any time, 55.07% of smokers were smoking at home only. Nearly half of the smokers have tried to quit. Regarding symptoms suffered, 31.9% have teeth discoloration, 18.8% have changes in mouth odor, and 16% have shortness of breath. Both dry mouth and night cough were encountered in14.5%, while only 13% have voice changes.

Table 1: Socio-demographics of sample

Variables	No.	%
Age class		
20-29	237	52.7
30-39	170	37.8
+40	43	9.6
Marital status		
Ever married	277	61.6
Unmarried	173	38.4
No of children		
0-2	311	69.1
3-5	99	22
+3	40	8.9

Education		
Post graduate	152	33.8
Bachelor	298	66.2
Field of work		
Doctors	238	52.9
Dentist	117	26.0
Pharmacist	95	21.1
Place of work		
PHC	89	19.8
Hospital	250	55.6
Health institute	111	24.7
Years of service		
<5	225	50.0
>5	225	50.0
Total	450	100

Table 2: Social smoking environment

Smoking status	No family history	Parents and siblings	Husband and friends	Tot
Smoker	5(7.3)	31(44.9)	33(47.8)	69 (15.3%)
Non smoker	106(27.8)	157(41.5)	118(31)	381 (84.7)
Total	111	188	151	450 (100)

X^a 15.166 df 2 P=0.001

Table 3: Smoking status according to socio-demographic & occupational variables of sample studied

	Smoker	Non smoker	Total	X2	df	p
Age						
20-29	41(59.4)	196(51.4)	237			
30-39	21(30.4)	149(39.1)	170	1.899	2	0.387
+40	7(10.2)	36(9.5)	43			
Marital status						
Ever married	44	233	277			0.681
Non married	25	148	173	0.169	1	
No of children						
0-2	49	262	311			
3-5	13	86	99			0.757
+5	7	33	40	0.557	2	

Cont... **Table 3: Smoking status according to socio-demographic & occupational variables of sample studied**

Education Post graduate bachelor	 18 51	 134 247	 152 298	2.155	1	0.142
Field of work Doctors dentists pharmacists	 35(50.7) 22(31.9) 12(17.4)	 203 95 83	 238 117 95	1.692	2	0.429
Place of work PHC Hospital Health institute	 8 42 19	 81 208 92	 89 250 111	3.446	2	0.179
Years of service <5 >5	 36 33	 189 192	 225 225	0.154	1	0.695

Table 4: Reasons of smoking and non-smoking

Smoking status	Reasons	No.	(%)
Smokers	 Enjoy Stress With smoker group Habit Adult feeling	 37 21 7 3 1	(53.6) (30.4) (10.1) (4.3) (1.5)
Subtotal		69	(15.3)
Non-smokers	Health risk	246	(64.6)
	Belief	83	(21.8)
	Cultural barrier	46	(12.07)
	Husband refusal	6	(1.6)
Subtotal		381	(84.7)
Total		450	(100)

Table 5: Smoking setting & consequences

Characteristic		No.	(%)
Type	Cigarette	45	65.3
	Nargileh	24	34.7
Time	Anytime	50	72.4
	Morning	0	0
	At night	19	27.6

Cont... **Table 5: Smoking setting & consequences**

Place	At home	38	55.07
	Workplace	2	2.8
	Anywhere	29	42.03
Try to quit	Yes	38	55.07
	No	31	44.93
Symptoms	Dry mouth	10	14.5
	Teeth discoloration	22	31.9
	Mouth odor	13	18.8
	Voice change	9	13
	Night couth	10	14.5
	Shortness of breath	11	15.9

Discussion

Tobacco smoking is responsible for >7 million deaths per year, nearly 80% of which occur in low- and middle-income countries[8]. The percentage of smokers among studied sample was relatively high compared to (1.9%0) and (13.2%) in Hilla city/Iraq [9] and India[10] respectively.

Doctors show the highest percentage of smokers (50.7%). While the higher percentage of smoking (52.7%) was in (20-29) years old. This may be due to the fact the young female medical providers have liberal thoughts about smoking and do not consider it as stigma, besides the openness to neighboring countries, in addition to spending more time on internet. In this study the minority of the sample were postgraduate, this due to the fact that the majority of the sample were young in age. About (55.6%) of the sample are working in hospitals this also can be due to the same reason which is the smallest age of the doctors, dentists and pharmacists the higher possibility of working in hospitals as interns or permanent resident. That is also applicable on years of service.

Coming to the smoking environment, it was the only significant variable associated with smoking status. This agrees with a study in Iraq[11] Saudi Arabia[12] and USA[13].This may be explained by the effect of negative socialization, and the influence of friends and family on individuals. About 45% of smokers have parents or siblings who are smokers. While about 48% of smokers have husband or friends who are smokers. This agree with a study in USA in which they found that having two ever-smoking parents, in comparison to zero or one, was associated with higher nicotine dependence scores, cigarettes per day[14] which may be explained by the strong influence of family and friends on customs and temperament.

The present study reveals that the higher percentage of smoking reason (53.6%) was enjoyment. This agrees with a study in Saudi Arabia[12]. This may be explained by the fact that doctors' life is stressful.

Regarding the smoking characteristics about (65.3%) of smokers smoked cigarettes. About half of them smoked at any time while 55% smoked at home. Smoking at home is more convenient for female doctor's giving privacy, and is more suitable than morning medical work, or afternoon clinic work. Nearly 55% of smokers have tried to quit. This is higher than a study in Armenia.

Coming to the side effects of smoking reveled in this study , the highest was (32%) teeth discoloration , the rest of side effects were change of mouth odor, shortness of breath, dry mouth ,night cough and voice changes.

Conflict of Interest – **Nil**

Source of Funding- **Self**

Ethical Clearance – **Not required**

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Retrospective Study of Acute Pediatric Intoxication Cases by Household Products Presented to the Poison Control Center of Ain-Shams University Hospitals

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Abstract

Background: Acute poisoning in children is a crucial pediatric emergency and may be a worldwide problem. This study aims to acknowledge the incidence of acute poisoning by household products in children regarding demographic factors, common clinical presentation and outcome of management.

Methods: this is often a descriptive retrospective study conducted on patients admitted to the Poison Control Centre of Ain-Shams University Hospital. The duration of the study was one year, from the beginning of January, 2016 till the top of December, 2016. the entire number of cases was 846 cases collected and analyzed regarding the demographic data, condition of poisoning, common clinical presentation, and management plan. Data was analyzed using computer software package SPSS 15.

Results: a complete of 846 cases were reviewed, the varied age groups involved ranged from but one year to 18 years, with a mean age of 10.22 ± 6.83 years. Most cases were females (67 %), living in urban areas (52.4 %) and therefore the majority of cases were accidental (74 %). the foremost common offending agent was pesticides (71%). Most of the patients were vitally stable on admission and therefore the commonest clinical presentation was gastrointestinal symptoms (31.3%). Most of cases received medical treatment within the inpatient wards (80.5%) and (96.7%) improved while (3.3 %) died.

Conclusions: Acute poisoning by household products is common among adolescents and pre-school age children. Pesticides were liable for the bulk of cases. Supportive and symptomatic therapy is that the main method for treatment.

Keywords: *acute poisoning, children, household products, pesticides.*

Introduction

Acute poisoning is a common situation in the emergency departments (EDs) all over the world and involves high medical attention and significant costs.[1] Childhood poisoning is a significant public health problem and a preventable cause of morbidity and mortality.[2]

The most important difference between pediatric and adult poisoning is types of agents. In adults, higher percentages of poisoning cases are due to psychopharmacologic drugs (sedatives, tranquilizers and antidepressants), whereas in children, there is a much higher frequency of exposure to household items and personal care products and plants.[3]

Many studies indicated that a variety of social and demographic factors like family size, socioeconomic condition, attention to child as well as storage place of poison are important risk factors which significantly influence the acute household poisoning cases in children.[4]

Accidental poisoning has a strong age predilection. This problem is particularly common in toddler and

older children in the age group of 1-5 years. Children of this age group have increased tendency to eat or drink any object or substance due to strong oral orientations. They are also very keen to explore the environment.[5]

Materials and Methods

This is a descriptive retrospective study. Data of all acute toxicity cases by household products among children (total number of cases was 846), who were admitted to the Poison Control Centre of Ain-Shams University Hospital (PCC- ASUH) during one year study period, from January, 2016 to December, 2016 were collected and analyzed. Cases were categorized according to age, sex, residence, time of poison exposure, manner of toxicity, type of poison, presentations, management plan and final outcome of the cases. Patients were divided into 4 age groups; these are infancy (< 2 years), preschool age (2-6 years), school age (7-12 years) and adolescents (13-18 years). Residence of the patients was also classified into urban and rural areas. According to type of poison, the patients were also divided into 4 groups; these are pesticides group, cleaning and disinfectant products group, hydrocarbons group and miscellaneous group. General management steps (ABCs), Specific measures like decontamination, gastric lavage, administration of activated charcoal and antidotes were also recorded. Data was coded and entered using the statistical package for Social Sciences (SPSS version 15). The data were summarized using a descriptive frequency and percentage for quantitative values. Relation between data grouped was tested by *Chi-Square* test for quantitative variables. Statistical differences (P-values) less than or equal to 0.05 were considered statistically significant. Data was collected after obtaining consent from the chef of the PCC of ASUH and from the ethical committee of scientific research, Faculty of Medicine, Beni-Suef University.

Results

This study was conducted on 846 children. The various age groups involved ranged from less than one year to 18 years, with a mean age of 10.22 ± 6.83 years. The adolescent age group had the greatest representation (52.7 %), followed by pre-school age children (37.5 %), infants (6 %), and school age children (3.8 %) figure (1). Females were more common than males (67 %) figure (2). Most of children were living in urban areas (52.4 %).

As regard the type of agents involved, the pesticides group was the most common (71%) and was distributed as follows: rodenticides (66.4%), insecticides (33.6%). Followed by cleaning and disinfectant products group (18.9%) which was distributed as follows: bleaches (70%), sulfuric acid (15%), carbolic acid (6.2%) and flash (8.8%).Then the group of hydrocarbons (5.2%) showed that the cases of kerosene were 95.5% and those of other hydrocarbons were 4.5%. Lastly the miscellaneous group (4.9%) and was distributed as follows: cosmetics and personal care products were 92.7% and others were 7.3% figure (3).

Regarding the manner of toxicity, the majority of cases were accidental (74 %) while suicidal poisoning was in (26 %). Accidental poisoning was more common than suicidal among all age categories and was more common in males (85.7%) than females (68.3%) while suicidal poisoning was more common in females (31.7%) than males (14.3%). Suicidal cases were reported only during Adolescence table (1). It was found that all types of household products toxicity was more common in females than males except for hydrocarbons group; males were more common than females *(66%) Vs (34%)* table (2).

Regarding the clinical manifestation, the most common clinical presentation was gastrointestinal symptoms (31.3%) figure (4), neurological symptoms was in (22.3%) of patients, respiratory symptoms (10.8%), Cardiovascular symptoms (3.3 %), Multiple symptoms (5 %) and others (1.8 %).216 (25.5 %) patients were asymptomatic.

Most of the patients were vitally stable on admission and had normal serum sodium, potassium and blood glucose level at presentation time. However, hypokalemia was detected in (26.7 %) figure (5).

According to the place of admission, the study revealed that most patients received medical treatment in the inpatient wards (80.5%) followed by the intensive care unit and those observed in emergency department without admission (15.7% and 3.8%) respectively table (3).

Treatment of cases mainly depends on supportive and symptomatic treatment, elimination of the poison from the body and the use of antidote if available. For airway and breathing, oxygen was used in (4.8 %), endo-tracheal tube was inserted in (5 %) and only (3.4 %) of patients were put on mechanical ventilation. For circulation, majority of patients received IV fluids (97.3 %), steroids (11.7 %) and dopamine (0.9 %). For symptomatic ttt, antibiotics were used in (0.2 %), anti-emetics (56.8 %), H2 blockers (29 %), bicarbonate (8.9 %), sedative hypnotics (1.9 %) and epanutin (0.1 %).

Regarding GIT decontamination and the use of physiological antidote, Activated charcoal was used in (5 %) of patients and Gastric lavage (13.1 %). Antidotes were given to treat 42.2 % of cases. Atropine was the most common antidote used in 26.5 % of cases, Toxoguonin (15.4 %) and NAC (0.3 %).

Regarding the outcome of the patients, (96.7 %) improved when received medical treatment and discharged while (3.3 %) died. The highest mortality was in hydrocarbons group (9.1 %) followed by pesticides group (3.3 %) then cleaning & disinfectant products group (2.5 %).

Discussion

The demographic data of the present study revealed a highly significant increase within the incidence of acute poisoning by household products among patients in Adolescence period aged 13-18 years (52.7%) followed by Pre-school group aged 2-6 years (37.5%) an equivalent as observed in other studies.[6,2] the bulk of cases were females (67%), while males were (33%) this is often almost like other studies.[7] Children belonging to urban areas were more exposed (52.4%) compared to those in rural areas (47.6%) this might flow from to the very fact that mothers in populated area are busier in their jobs and resulting in neglect of their child during this area. The toxic agents can also be more available within the cities than within the rural areas.[8] this study indicated that the pesticides group was the foremost common explanation for poisoning (71%) followed by cleaning and disinfectant products group (18.9%) These results are approximately almost like other studies[9]. Regarding time of poisoning, most of poison cases were in evening (46 %) then afternoon (32 %) This agrees with other studies.[10,11] Accidental poisoning was more common than suicidal among all age categories while suicidal poisoning was more common in females (31.7%) than males (14.3%). These results agreed with other studies.[12] The bulk of patients were vitally stable. Gastrointestinal symptoms (vomiting, abdominal colic, diarrhea, dysphagia & hematemesis) were the foremost common symptoms (31.3%) followed by neurological symptoms (22.3%) These results are almost like previous study.[5] The majority of patients had normal sodium, potassium and blood sugar level. However, hypokalemia was detected in (26.7 %).[13] Most of patients received medical treatment within the inpatient wards (80.5%) followed by the medical care unit and people observed in emergency department without admission (15.7% and 3.8%) respectively.[14] activated carbon was utilized in (5 %) of patients and lavage (13.1 %). Antidotes got to treat 42.2 % of cases. Atropine was the foremost common antidote utilized in 26.5 % cases, Toxoguonin (15.4 %) and NAC (0.3 %) (15). while 28 (3.3 %) of our patients died, (96.7 %) improved when received medical treatment an equivalent as observed in other studies.[16]

Conclusion

Acute poisoning is a crucial explanation for emergency unit admissions. The incidence of poison exposure was highest among adolescents and pre-school age children. Intentional poisoning was more common in older girls and accidental poisoning was more common in younger boys. Pesticides and household cleansing products were liable for the bulk of cases of poison exposure. Gastrointestinal symptoms were the foremost common clinical presentations in acute toxicity by household products. In most of cases, treatment was non-specific, including general decontamination and supportive-symptomatic therapy. The utilization of physiological antidote is restricted to pesticides toxicity.

Funding : Not applicable as no fund was obtained for the study.

Availability of data and materials Please contact author for data requests

Authors' contributions

All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the chef of the poison control Centre of Ain-Shams University hospitals to collect the data from the archives of the patients' files in the Centre.

Consent for publication : Not applicable as no individual data, images or videos were included in the study.

Conflict of Interest: Nil

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Maternal Comorbidities Associated with Preterm Deliveries in Comparison with Full Term Delivery in Al-Zahraa Teaching Hospital in Al Najaf City

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Abstract

Background: Preterm birth is one of the major conditions that affect on infant mortality and morbidity, many of maternal comorbidities effect on the fetus outcome, in this study we evaluate some of maternal condition that effect on preterm birth and compare them with full term birth to know the most common factors associated with this condition to decrease the rate of preterm birth and reduce neonatal mortality and morbidity

Methods: A case control study was conducted at first of April to thirty of September 2018, in Al Zahra Teaching Hospital in Al Najaf City, 300 delivered pregnant women were participated divided to 100 cases as preterm delivery women and 200 controls as full term deliver women enrolled in the study, maternal comorbidities were recorded and binary regression analysis was used for analysis of the study.

Results: The study show many significant association between preterm birth and maternal risk factors include, urinary tract infection (OR = 7.32), lower number of antenatal visit (OR=2.52), interval between pregnancy ≤2 year (OR =1.973), premature rupture of membrane (or =6.55), oligohydramnios (OR =6.55), gestational diabetes (OR =3.45), abruptio placentae (OR = 5.06) and previous preterm labor (OR=3.68).

Conclusion: Based on the results in the study the most determinants that affect on preterm birth were urinary tract infection, premature rupture of membrane and abruption placenta.

Keywords: *Antepartum hemorrhage, Gestational Diabetes mellitus, Gestational Hypertension, Premature rupture of membrane, Preterm birth, maternal comorbidities, fetus outcome, oligohydramnios, abruptio placentae*

Introduction

Preterm delivery defined by The World Health Organization (WHO) as infant delivered at time below 37 completed weeks of gestation. It was divided into the following categories depending on mother gestational age, extremely preterm (<28 weeks), very preterm (28–<32 weeks), moderate or late preterm (32–<37 completed weeks of gestation [1].

An about fifteen million babies are deliver too early every year. Nearly one million children die every year because of the complications of preterm birth [2].

Preterm birth (PTB) considered as a major cause of morbidity and mortality and its percentage are increasing with time in many countries [3, 4].

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The majority of global preterm births occur in Asia and Africa with (85%), where the health systems are inadequate and weak [5, 6].

The rate of mortality, morbidity and the costs of Preterm labor are higher at lower gestational ages, in babies that survive, the risk is rise in form of short – and long term morbidity [7,8].

Obesity may not directly lead to preterm birth [9] however; it may associate with diabetes and hypertension which are risk factors by them [8]. Marital status is also associated with risk for preterm birth[10]. Pregnancy outside of marital status was associated with a 20% rise in adverse outcomes.[11]

Subfertility is another factor associated with preterm birth, Pregnancies after used in vitro fertilization confers a high risk of preterm birth after more than 1 year of trying [12].

A number of systemic maternal bacterial infections are associated with preterm birth this including pneumonia, appendicitis, pyelonephritis[13].

In study done in Iraq showed that risk of preterm birth increase with history of multiple pregnancy with (OR=7.5), history of cervical incompetence with (OR=4.7), and history of abortion with (OR=6.3) in comparison with pregnant women did not had previous history to such condition, heavy manual work with (OR = 1.70), and direct trauma to the abdomen (OR = 3.76) were also significantly associated with preterm birth[14].

A study done in Iran to measure risk factors of preterm birth found that history of preterm rupture of membrane, preeclampsia, and multiple pregnancies had increased risk of preterm birth with odd ratio equal 5.1, 4.6, and 17.4 respectively. In the same study the investigator found history of infertility and previous history of abortion were not statistically significant with preterm birth. [15]

Another studies done in Ethiopia revealed that many factors associated with preterm birth include preterm rupture of membrane, maternal age more than 35 years old , poor antenatal care, and infection of pregnant women with HIV[16,17].

A case–control study done in western part of China appeared that number of antenatal care four or less are more significantly associated with preterm birth with (OR=4) in relation to pregnant with adequate antenatal visit, while income of family, age of pregnant mother, and level of education were not significantly associated with preterm birth[18].

In Northwestern Russia study was investigate associations between preterm birth and selected maternal factors and found young pregnant with age (<18 years) or older (≥35 years) , underweight , obese mothers, smoking status, abuse of alcohol and history of diabetes mellitus or gestational diabetes were more likely associated with preterm birth[19].

Approximately 45–50% of preterm deliveries are without cause, 30% are caused by (PROM) and other 15–20% is due to indicated or elective preterm deliveries. [20]

Although many years of research to determine the etiology, epidemiology, and management of preterm birth. The incidence of it has continued to increase. There are a lot of hypothesis found to explain the increase in preterm as a technology of assisted reproduction and the desire of obstetricians to use elective delivery of infant of pregnant in whom medical, fetal, or obstetrical complications happen preterm[21, 22, 23, 24].

Subjects and Methods:

Study design:

A case control study.

Study setting and time:

Study was carried out in Al Najaf city and data were collected from post delivery ward in Al-Zahraa Teaching Hospital which is a major teaching and referral hospital for obstetrics and gynecology receive pregnant from central and peripheral area, handles with uncomplicated and complicated deliveries , data collected in period between 1st of April 2018 to 30th of September 2018.

Sample size:

To achieve the aim of the study, a case control study use with sample size calculated according to equation below:

Sample size= $\frac{r+1}{r}\frac{(P^*)(1-P^*)(Z_\beta+Z_{\alpha/2})^2}{(P_1-P_2)^2}$

Data collection:

The inclusion criteria include:

- Female at reproductive age 15-45 years.
- Singleton pregnancy determined by ultrasound.
- Pregnant know her LMP or had U/S at 1st trimester.

Exclusion from this study:

- Multiple gestations.
- Those who are using assisted conception.

Statistical Analysis

Data were entered, and analyzed using the statistical package for social sciences SPSS version 25.

Results

The parity of the women in both study groups showed no significant association between both groups, 34% vs. 26.5%, respectively in nulliparous women, and 66% vs.73.5% respectively in multiparous women (P= 0.224) with CI 95% of OR=(0.84 - 2.40).

The interval between pregnancies was 2 years or less in 44 women (66.7%) out of the 66 parous women (parity one or more) in preterm group and it was more than 2 years in the remaining 22 (33.3%), while the corresponding frequencies in the term group were 74 (50.3%) and 73 (49.7%) out of 147 parous women in this group respectively, statistically significant difference had been found (P= 0.027) (OR=1.97). History of preterm labor was significantly frequent in preterm than term group, 24.2% and 12.9%, respectively, (P=0.039) with (OR=2.15).

Previous cesarean sections (CS) was not significantly different between studied groups, 37.9% in preterm and 36.1% in term group, (P>0.05), CI 95% of OR= (0.59 - 1.97).

Number of antenatal visit was significantly lower in preterm than term group (P=0.037) where 21% of women in preterm had no antenatal visit compared to only 14% in the term group, additionally, 35 women (35%) in the preterm group had 1-3 visit compared to 58 (26.5%) in the term group while 44% preterm women and 59.5% term women had 4 or more visits. All findings regarding the obstetrical history of the studied groups are demonstrated in (Table 1).

Table 1. Obstetrical history of the studied groups

Variable		Preterm (N=100)		Term (N=200)		P. value	OR	CI 95%
		No.	%	No.	%			
Parity	Nulliparous	34	34.0	53	26.5	0.224	1.42	0.84 - 2.40
	Multiparous	66	66.0	147	73.5			
Interval between pregnancies*	≤ 2year	44	66.7	74	50.3	0.027	1.97	1.07 - 3.61
	>2year	22	33.3	73	49.7			
Previous preterm labour	Yes	16	24.2	19	12.9	0.039	2.15	1.02 - 4.52
	No	50	75.8	128	87.1			
Previous CS	Yes	25	37.9	53	36.1	0.798	1.08	0.59 - 1.97
	No	41	62.1	94	63.9			
Number of antenatal visit	None	21	21.0	28	14.0	0.037		
	1-3	35	35.0	53	26.5			
	4 and more	44	44.0	119	59.5			

*Primi women were excluded from calculation

In (Table 2) no significant differences had been observed between both groups regarding the mode of delivery or the sex of the neonate, (P>0.05) with CI 95% of OR= (0.75 - 2.02) and (0.41 - 1.08) respectively. Furthermore, all neonates in preterm group had birth weight of < 2500 gm. compared to only 6 (3%) in term group with a statistically significant difference (P<0.001).

Table 2. Mode of delivery and neonatal characteristics of the studied group

Variable		Preterm (N=100)		Term (N=200)		P. value	OR	CI 95%
		No	%	No.	%			
Mode of delivery	CS	41	41.0	72	36.0	0.399	1.23	0.75 - 2.02
	VD	59	59.0	128	64.0			
Sex of neonate	Male	48	48.0	116	58.0	0.101	0.66	0.41 - 1.08
	Female	52	52.0	84	42.0			
Weight of neonate (gram)	< 2500	100	100.0	6	3.0	< 0.001		
	≥ 2500	0	0	194	97			

Table 3 shows the comorbidities reported in both studied groups; where no statistically significant differences had been found in the frequency of chronic hypertension; 3% vs. 1.5%, (P>0.05), CI 95% of OR=(0.46 - 11.76) , gestational hypertension found in 14% and 11% of preterm and term groups, respectively, (P>0.05), CI 95% of OR=(0.72 - 3.04). Preeclampsia/eclampsia status was significantly more frequent in preterm group, (8%) compared to only (0.5%) in term group (P = 0.001) with (OR=18.56). Presence of cardiovascular disease was not significantly different between the studied groups, (P>0.05). Preexisting diabetes mellitus was not significantly different between both groups, (P>0.05), CI 95% of OR= (0.11 - 13.14), while gestational diabetes mellitus was significantly more frequent in preterm group (19%) than term group (10%), (P=0.001) with (OR=4.46). Frequencies of thyroid diseases and anemia were not significantly different between both groups (P >0.05) , CI 95% of OR= (0.22 - 8.33) and (0.67 to 1.76) for hypothyroidism and anemia respectively. Frequency of antepartum hemorrhage due to abruptio placentae was significantly higher in preterm than term group; 27% vs. 6%, (P=< 0.001) (OR=6.07) , APH due to placenta previa was not significantly different between groups, 7% in preterm and 5% in term group (P>0.05), CI 95% of OR=(0.69 - 5.16). Preterm rupture of membrane was significantly more frequently occurred in preterm group, (25%) than in term group (1.5%) (P<0.001) (OR=21.89). Polyhydramnios amniotic fluid status was not significantly different between both groups (P>0.05), CI 95% of OR= (0.56 - 6.39) while oligohydramnios was significantly more frequent in preterm than term group, 15% vs. 6%, respectively (P = 0.016) (OR=2.48).

Cervical incompetence was significantly more frequent in preterm group, (11%) compared to only 3% in term group, (P=0.005) (OR=4). Uterine abnormalities were not significantly frequent in preterm compared to term group, 2% vs. none, respectively (P=0.209). No significant difference between both groups in the presence of genital infection (P>0.05), CI 95% of OR= (0.57 - 1.49). Finally, higher proportion, 62%, of women in preterm group had (UTI) compared to 21.5% among women in term group, the difference was statistically significant, (P<0.001) (OR=5.96).

Table 3. Comorbidities reported among the studied group

Variable				Term (N=200)		P. value	OR	CI 95% of OR
		No.	%	No.	%			
Hypertension	Chronic	3	3	3	1.5	0.56	2.32	0.46 - 11.76
	Gestational	14	14	22	11	0.38	1.48	0.72 - 3.04
	Preeclampsia/eclampsia	8	8	1	0.5	0.001	18.56	2.28 - 151.03
	None*	75	75	174	87		-	-
Cardiovascular disease	Yes	1	1	0	0	0.157	-	-
	No	99	99	200	100		-	-
Diabetes mellitus	Preexisting	1	1	2	1	0.61	1.18	0.11 - 13.14
	Gestational	19	19	10	5	0.002	4.46	1.99 - 10.03
	None*	80	80	188	94	*	*	*
Thyroid disease	Hyperthyroidism	2	2	0	0	0.21	-	-
	Hypothyroidism	2	2	3	1.5	0.89	1.37	0.22 - 8.33
	None*	96	96	197	98.5	*	*	*
Anemia	<11gm/dl	56	56	108	54	0.734	1.08	0.67 to 1.76
	≥11gm/dl	44	44	92	46			
APH	Abruptio placentae	27	27	12	6	< 0.001	6.07	2.91 - 12.67
	Placenta previa	7	7	10	5	0.329	1.89	0.69 - 5.16
	None*	66	66	178	89	*	*	*
Preterm rupture of membrane	Yes	25	25	3	1.5	< 0.001	21.89	6.42 - 74.64
	No	75	75	197	98.5			
Amniotic fluid	Polyhydramnios	5	5	6	3	0.474	1.9	0.56 - 6.39
	Oligohydramnios	15	15	12	6	0.016	2.84	1.27 - 6.35
	Normal**	80	80	182	91	*	*	*
Cervical incompetence	Yes	11	11	6	3	0.005	4.00	1.44 - 11.15
	No	89	89	194	97			
Uterine abnormality	Yes	2	2	0	0	0.209	10.17	0.49 - 214.04
	No	98	98	200	100			
Genital infection	Yes	44	44	92	46	0.734	0.92	0.57 - 1.49
	No	56	56	108	54			
UTI	Yes	62	62	43	21.5	< 0.001	5.96	3.52 - 10.10
	No	38	38	157	78.5			
*None used as a reference subgroup in comparison **normal used as reference subgroup								

Further analysis had been performed to assess the predictor factors of preterm labors, therefore, the factors

that appeared to be significantly different between both groups were entered as independent factors (covariates) in the bivariate regression analysis, and the status of birth (term or preterm) used as dependent variable and the test was run. Results of binary regression analysis and odds ratio (OR) are shown in (Table 4), where eight factors still significant and were the predictors associated with preterm labor after adjustment of other variables; these are interval between pregnancies less than 2year (OR = 1.973), previous preterm labor (OR= 3.68),lower no. of antenatal visit (OR =2.52), gestational diabetes mellitus (OR = 3.45), Abruptio placentae (OR = 5.06), preterm rupture of membrane (OR =6.55), oligohydramnios (OR = 3.53) and urinary infection (OR = 7.32) , in all these factors, (P<0.05). Other factors showed no significant association (P>0.05).

Table 4. Results of binary regression analysis for the maternal factors associated with preterm labor

Variable in the regression equation	B	Odds ratio (OR)	95% C.I. for (OR)		P. value
			Lower	Upper	
Interval between pregnancies (shorter)	0.680	1.973	1.077	3.614	0.028
Previous preterm labour	1.302	3.68	1.21	11.20	0.022
Lower no. of antenatal visit	0.926	2.52	1.46	4.37	0.001
Hypertension /preeclampsia-eclampsia	0.344	1.41	0.72	2.23	0.246
gestational DM	1.239	3.45	1.17	10.22	0.025
Abruptio placentae	1.622	5.06	2.48	10.34	0.001
Premature rupture membrane	1.879	6.55	1.34	32.06	0.020
Oligohydramnios	1.262	3.53	1.43	8.74	0.006
Cervical incompetence	0.259	1.30	0.21	8.04	0.781
Urinary tract infection	1.990	7.32	2.97	18.04	0.001

Discussion

In current study there is no significant association between PTB and parity , similar result present in Iraq [14], other study done in Iran had different result[25]. Also study done in Cairo found mothers with first baby had higher risk of preterm birth with (p=0.018) [26]. other study done on preterm births which found that nulliparity is an important risk factor for preterm delivery in South Nigeria [27]. The discrepancy of finding in different countries may be attributed to the difference of the factors between the countries.

Interval between pregnancies of ≤ 2 year was found 2 fold more likely to cause PTB. This agree with study in Iran [25], these presentation may suggest that increase spacing between pregnancies could help to prevent the adverse pregnancy outcomes[28] ,while in Palestine no association present between PTB and interval between pregnancy[29].

The study also revealed a significant association of cervical incompetence and previous preterm delivery to cause PTB and this agree with study done in Palestine [29], and this could be the fact that the cervix is unable to maintain pregnancy to term.

In this study there is a significant association between number of antenatal visit (no visit) and the PTB in which 21% of preterm mother had no antenatal visit in comparison with 10% of full term mother, this agree with study done in Iran, with (p0.036) [25]. In a study done in Nigeria on the determination of preterm births, no booking of pregnant women in antenatal care program was found to be one of the strong determinants[30], while different result present in Kenya that found no association with preterm birth and attendance to antenatal care (p=0.621)[31].

The current study also investigate the possible association of preterm birth and history of HTN, in which preeclampsia/eclampsia was 19 fold more likely to cause PTB, while chronic and gestational hypertension not significantly associated with PTB, this agree with result in Iran found that the risk of preterm labor in mothers suffering from preeclampsia is 4.6 times higher than in other mothers[32]. Also other study in Tehran found preeclampsia and gestational HTN strongly associated with preterm birth [33]. Study done in japan demonstrated that the risk of preterm labor is higher in mothers suffering from preeclampsia or chronic hypertension [34]. The chronic and gestational HTN not appear as a risk factor this may attributed to well control of HTN in participant women.

In this study, from a statistical significance viewpoint, anemia was not associated with PTB p-value= (0.734), this agree with study in Palestine (p value=1.0) [29],also with study in Iran (P= 0.47) [25]. Disagreement appears in study done in Ethiopia [35] and in Cairo[26], the difference in significance of result may be attributed to degree of severity of anemia in studied women.

Previous cesarean section not significantly associated with pregnancy outcome (p=0.798), regarding to uterine abnormality, in this study was no statistically significant (P < 0.209) with PTB, and this result different from study done in Tehran [33]. Also no significant association between cardiovascular disease with (p=0.157) and thyroid disease (hyperthyroidism, hypothyroidism) with (p=0.208, p=0.889) respectively and pre term birth. No association in these factors may be due to need larger sample and more early investigations and fellow up.

The effect of gestational diabetes, it 4 fold increase risk related to preterm outcome p(0.001) while preexisting diabetes not significantly associated with preterm birth with (p=0.618). This agree with study done in china, found GDM is a significant risk factor with (OR=3.441) [36], and disagree with study done in Frances that found, pre-existing diabetes was strongly associated with PTB as a comparison with gestational diabetes [37]. In study done in al Mosul, no significant association present between diabetes mellitus and preterm birth [14]. In this study the preexisting diabetes not a risk factor, this my due to small number of participants detected .

Regarding antepartum hemorrhage the study found a significant association between placental abruption with preterm delivery, in contrast with placenta previa in relation with preterm delivery. Results also agree with study done in Iran that found no significant association between placenta previa and preterm birth [25]. Other study done in Palestine appeared that placenta abruption and placenta previa were found to be a significant risk factors for preterm birth[29]. In Nigeria study found a complication of pregnancy including antepartum hemorrhage was significantly associated with preterm birth [38]. Other research in Mosul reported that antepartum hemorrhage was not considered as a risk factor for preterm birth [14]. Placenta previa not significantly affect preterm this may attributed to the type of placenta previa like in study done by Dola et al. Found that preterm birth was more happened in pregnant women with complete placenta previa[39].

Conclusion

- Maternal Urinary tract infection is a significant factor effecting PTB, fellow by PROM and abrubtio placentae.

- There is a strong association between preterm birth and oligohydramnios, gestational DM, no antenatal visit, previous preterm labor and short interval between pregnancies.

Ethical Clearance- Taken from The Institution's Ethical Committee approval

Source of Funding- Self

Conflict of Interest – nil

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