INTRODUCTION

According to the World Health Organization (WHO) document of 1972, the term congenital anomalies has to be limited to structural defects at birth) ***(Patel et al., 2005).*** Definition of congenital anomalies according to the WHO fact sheet of October 2012: are structural or functional anomalies and metabolic disorders present at birth ***(World Health Organization, 2012)***.

The universal incidence of congenital malformation is around 3% to 7% but the accurate percentage varies widely from country to country ***(Park et al., 2005).***

A better understanding and increased awareness about the epidemiology of children suffering from congenital anomalies is of high priority because of the maternal and child health indicators in healthy people ***(Cassell et al., 2010)***

According to the World Health Organization (WHO) report, about 3 million infants are born each year with major congenital anomalies. congenital anomalies found in about 3% of newborns, worldwide about 276000 babies die within one month after birth from congenital anomalies every year ***(WHO, Media center, 2015).***

Congenital anomalies may be discovered before delivery, at birth or long time after delivery, they may be minor as port wine navi, or severe defects as cleft lip or group of anomalies

affect multiple tissues, or Errors of metabolism present at birth. Congenital anomalies can be inherited or solitary, single or multiple, gross or microscopic ***(Moore et al., 2003).***

Most of the Congenital anomalies are thought to have a multifactorial inheritance caused by interactions between genetic and environmental factors which are generally unknown, these diseases are named complex diseases. This interaction between genetic and environmental factors lie behind the etiological heterogeneity of these anomalies, implementation of more researches about genetic-environmental interactions will result in better understanding of the biological mechanisms and pathological pathways that share in the development of complex congenital anomalies. On the light of this understanding more efficient measures can be developed to prevent these severe costly and often fatal anomalies ***(Zhu et al., 2009).***

Till now the accurate causes of 40% - 60% of congenital anomalies are unknown. Genetic conditions (chromosomal and single gene causes) are behind 15%-25% of congenital anomalies, environmental factors (maternal-related conditions, drugs or chemicals exposures) are responsible for 8%-12% and multifactorial inheritance are the cause of 20%-25% ***(Ekwere et al., 2011).***

Aim of the Work

This study aims to assess the frequency and distribution and associated risk factors of dismorphologic congenital anomalies in live newborns and stillbirths in Damietta general hospital in a period of one year (2016), and to evaluate their correlates, in order to identify the appropriate strategies for prevention.

REVIEW OF LITERATURE

Definition of congenital anomalies:

Congenital anomalies, congenital abnormalities, birth defects and congenital malformations are all terms used to express developmental disorders of the embryo and fetus. There are lots of separate anomalies which fall under these titles including structural, functional, metabolic and hereditary conditions. However, there is no single agreed system of classification of anomalies or indeed a single universally accepted definition of congenital anomalies ***(Kurinczuk et al., 2010).***

Classification of congenital anomalies:

Much of the literature used for describing congenital conditions predates genomic mapping, and structural conditions are always viewed separately from other congenital conditions. It is now known that there is a clear structural expression for many metabolic conditions, and there are genetic links for many structural conditions. Congenital conditions are usually classified and organized in a structural basis according to affected primary organ system. Many terms are used to express congenital anomalies. Some of these terms are also used to describe noncongenital conditions, and more than one term may be used to describe an individual condition. Congenital anomalies may be uni or bilateral, and different anomalies

usually coexist in an individual person, congenital anomalies are structurally classified into malformations, disruptions, deformities and dysplasias according to the causative mechanism of the defect. Syndromes and sequences and are also distinguishable types of congenital anomalies, The etiology of most congenital anomalies is multifactor, this means the cause is usually complex mixture of etiologic factors including genetic, environmental, and behavioral factors ***(CDC, 2014).***

Malformations are primary structural anomalies that take place during development of a tissue or an organ**,** and occur due to an abnormality during the developmental course. Malformations usually occur in the first trimester ***(Graham and Whichello, 2007).*** Some examples of malformations are: cleft lip and palate, congenital cardiac diseases, meningomyelocele and pyloric stenosis. Most of the single gene malformations are polygenic/multifactorial, in origin with a low risk of recurrence. The recommended treatment for correction is the surgical treatment. Many of malformation syndromes are consisted of defects in two or more systems and associated with mental retardation (Fig. 1). The risk of recurrence depends on the cause, whether the condition is due to a single gene defect, chromosomal defect, teratogenic cause or the cause is unknown ***(Purandarey, 2009).***

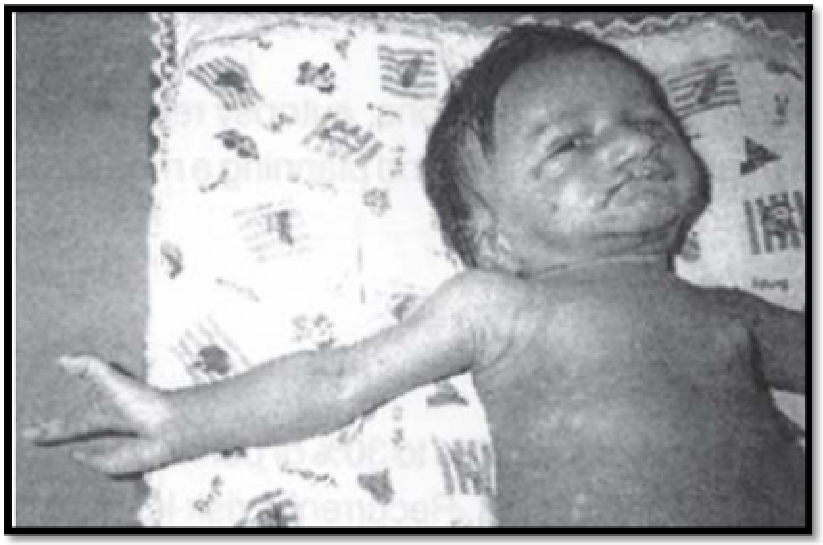

Figure (1): Multiple congenital anomalies ***(Purandarey, 2009).***

Disruption: describes a condition where the fetus has a normal development, and disruption in development takes place due to external factors (e.g., in amniotic band syndrome). various classes of disruption have been identified, including those occurring due to prenatal infections as (rubella, cytomegalovirus, and toxoplasmosis); chemical materials like (mercury, lead, alcohol, thalidomide, and cancer chemotherapeutic agents); immune conditions as fetal graft-versus-host disease; vascular defects; metabolic defects; hormones such as diethylstilbestrol; gestational disruptions, including implantation defects; and twinning disruptions, for example (acardia) that leads to reverse flow of blood from one twin into the other, the donor twin undergoing regressive or degenerative phenomena that may end in death ***(Opitz, 2007).***

Deformities due to abnormality of intrauterine moulding can occur because of maternal or fetal conditions. Hip joint dislocation, and clubfoot result from oligohydramnios. Fetus with abnormalities of the musculoskeletal system may have positional deformities. Multiple pregnancies or breech presentation can also cause deformities. Potter syndrome is associated with renal agenesis leading to oligohydramnios, which may result in pulmonary hyperplasia and fetal deformation ***(Purandarey, 2009).***

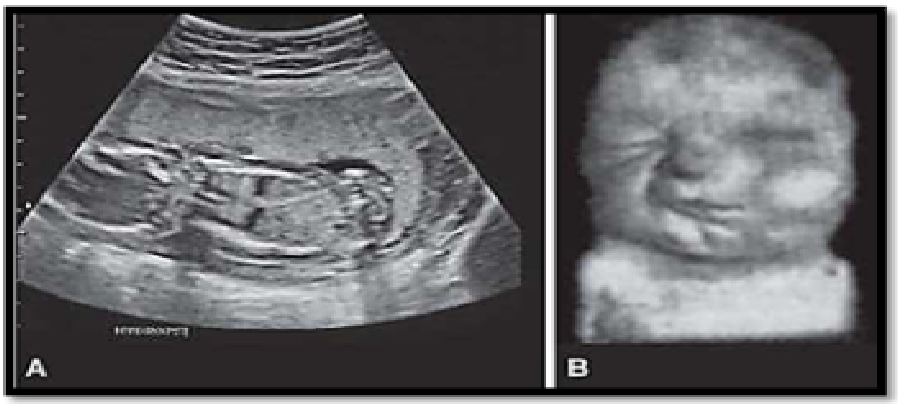

Figure (2): An example of a deformation is the potter syndrome. Note the severe oligohydramnios seen on ultrasound (A) and (B) a fetus with Potter syndrome ***(Purandarey, 2009).***

Dysplasia describes an abnormal organization of cells in a certain tissue and usually affects all parts of the body where that particular tissue is present. An example is thanatophoric dysplasia, which is a type of skeletal dysplasia, takes place as a result of mutations in the gene FGFR3, in this condetion all parts of the skeleton are affected. In ectodermal dysplasia, there

is also affection in tissues of ectodermal origin e.g hair, teeth and nails. Most dysplasias occur as a result of a single gene defect, there is a high recurrence risk for children and siblings, It takes place at the organ level due to defects in tissue development ***(Graham and Whichello, 2007)***. The term dysplasia is derived from Ancient Greek δυσ- dys-, "bad" or "difficult" and πλάσις plasis, "formation") to represent the abnormality of development or an epithelial anomaly of growth and differentiation of cells ***(Dorland's Medical Dictionary, 32 ed.).***

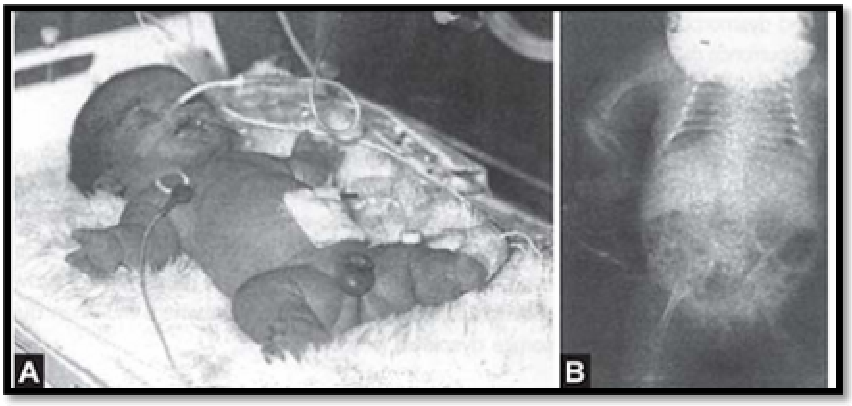

Figure (3): (A) Skeletal dysplasia in a new born (B) X-rays of the same infant showing shortening of the long bones and narrow thoracic cavity ***(Purandarey, 2009).***

Sequence is where a single site defect causes apparently unrelated anomalies as a result of a developmental cascade. Such as, in Potters syndrome due to chronic leakage of amniotic fluid or renal agenesis, oligohydramnios takes place which leads to fetal compression resulting in dysmorphology of

facial features, hip dislocation, pulmonary hypoplasia and talipus. The condition is perpetually fatal. As in spina bifida, blockage in the normal flow of cerebrospinal fluid can lead to hydrocephalus (Figs 4) ***(Purandarey, 2009).***

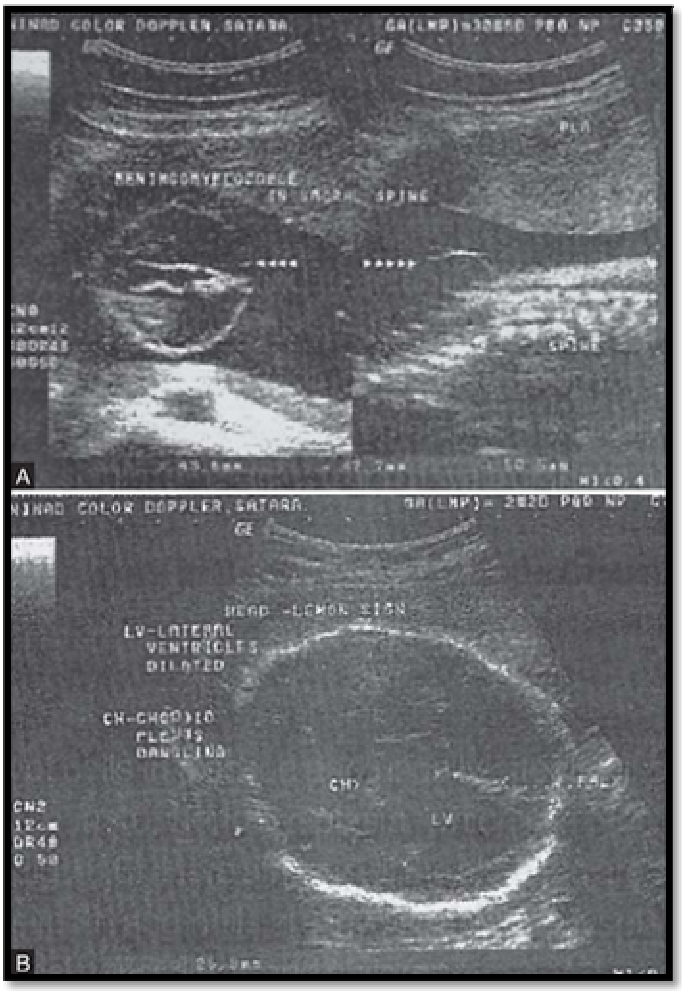

Figure (4): Ultrasound showing. (A) Meningomyelocele and (B) Hydrocephalus take place secondary to obstruction of the flow of CSF, as an example of a sequence ***(Purandarey, 2009).***

Syndrome: A syndrome is a group of medical signs and symptoms that are correlated with each other, and characterize a particular condition or abnormality (is applied to conditions where consistent patterns of abnormalities are seen as a result of an underlying cause), the term is derived from the Greek σύνδρομον, meaning (concurrence) ***(Dorland's Illustrated Medical Dictionary, 2012)***. In some conditions, a syndrome is so closely linked with a pathogenesis or cause that the words syndrome, disease, and disorder end up being used interchangeably for them. This is true especially in inherited syndromes. Such as, Down syndrome, Wolf–Hirschhorn syndrome, and Andersen syndrome are disorders with well known pathogeneses, so every syndrome is not just a group of signs and symptoms, in spite of the nomenclature of syndrome. In other conditions, a syndrome is not specific to only one disease. Such as, toxic shock syndrome can be due to a variety of toxins; pre-motor syndrome can be due to a variety of brain lesions; and premenstrual syndrome is not a disease but a group of symptoms, in the main a syndrome includes a numeral essential characteristics which when concurrent initiate diagnosis of the disease ***(Myers et al., 2014).***

There is some phenotypic variation in many syndromes both in individuals throughout life and between different individuals. This could be due to chromosomal abnormalities for example in Down's syndrome or without any chromosomal abnormality for example in Pierre Robin syndrome. a now there

is a computerized dysmorphology data base available for numerous malformation syndromes, which is of great help in estimation of prognosis and evaluation of recurrence risk**.**

Genetic association: The term genetic association may be used in conditions whereas an underlying genetic cause is suspected but not known, a (often just "association" in context). The definition: an association refers to the collection of signs and symptoms takes place in combination more frequently than would be likely by chance alone ***(Dorland's Illustrated Medical Dictionary, 2012).*** The known malformations have acronyms of the abnormalities, e.g. VATER association is consisted of of vertebral anomalies, anal atresia, trachea-esophageal fistula and radial defects. The acronym VACTERL is the VATER association yet includes cardiac defects and hydrocephalus. While CHARGE association includes (coloboma, heart defects, atresia of the choana, retardation of growth, genital anomalies, ear anomalies). Another example is the MURCS association: in this association there is: mullerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia is noted.

Twinning and multiple births: About 7.6% of the pregnancies result in twins, 6% of this percentage vanish and only 1.6% go to term. The incidence of malformations is higher in twins. Twins are classified into two groups - monozygotic (MZ) in which twins are identical and are developed from the fertilization of a single egg and a single sperm (single zygote)

within 3-8 days of fertilization. If the division takes place more than 2 weeks after conception there is a great possibility of conjoined twins. MZ twins often do not have a family history, MZ have the same genetic composition, and have the same sex though they may not be phenotypically identical. Sometimes Monozygotic twins can be dissonant for congenital malformations and genetic disorders. MZ female twins may have discrepancy in X-chromosomal inactivation. Dizygotic twins (DZ) are results of fertilization between two eggs and two sperms in the same ovulatory cycle. Dizygotic twins are like sibs and may have the same or different sexes. Multiple births occur in the same fashion. MZ twining is a chance occurrence while DZ twining is common and has three folds increased risk of recurrence. Multiple births as triplets or quadruplets, may be identical or non-identical. Twin researches are important in medical genetics. MZ and DZ twins are tremendous models for comparative studies of the impacts of genes and environment ***(Purandarey, 2009).***

Another classification of congenital anomalies

1) structural congenital disorders

A structural congenital anomalies denoting that certain part of the body is improperly formed or missing. Famous examples are congenital anomalies of heart structure (e.g: ASD, VSD, PDA) with rate of 1%. Another example is central nervous system anomalies (e.g.: microcephally, which means

that the size of brain is smaller than normal). The etiology of congenital anomalies is unknown. The surgical treatment is a usual treatment for structural, metabolic and functional congenital anomalies; but unfortunately in large proportion of cases, some symptoms still life long incurable. Once we understand the nature of congenital anomalies and know the accurate number of individuals living with congenital anomalies this will help in putting plans and programs for prevention and rehabilitation. Major congenital anomalies are structural changes in one or more parts of the body, They are present at birth. They can have a dangerous, harmful impact on the health, development, or functional abilities of the baby ***(Centers for disease control and prevention, 2017).***

a) Congenital anomalies of a limb (dysmelia): These include all forms of limbs anomalies, which can be:

1- Longitudinal anomalies (more common)

Longitudinal anomalies involve specific developmental abnormally (eg, complete or partial absence of the radius, fibula, or tibia). Radial ray deficiency which is the most common upper-limb anomaly, and hypoplasia of the fibula which is the most common lower-limb anomaly. About 66% of cases are associated with other congenital anomalies, including Adams-Oliver syndrome (aplasia cutis congenita with partial skull bones aplasia and terminal transverse limb anomalies), Holt-Oram syndrome, TAR syndrome (absent radius bone with

thrombocytopenia), and VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, radial aplasia, and limb anomalies).

2- Transverse anomalies

In this type, there is absence of all elements beyond a certain level, and the limb resembles an amputation stump. The most common cause is amniotic bands; the degree of deficiency varies according to the location of the band, and typically, this type of anomalies is not associated with other anomalies. The other causes are mostly underlying genetic syndromes for example Adams-Oliver syndrome and chromosomal abnormalities. According to the cause, infants With transverse or longitudinal limb anomalies infants may also have hypoplastic or bifid bones, synostoses, dislocations, duplications, or other bony anomalies; such as in proximal femoral focal anomalies, undevelopment of the proximal part of femur and -acetabulum. One or more limbs may be affected, the type of defect may differ in each limb. CNS anomalies are rare.

Polydactyly is the most common congenital limb anomaly, it is supernumerary digits. This anomaly is classified as: preaxial, central, and postaxial polydatyly. Preaxial polydactyly is an extra thumb or great toe. The picture range from a broad distal phalange or duplicated distal phalange to complete duplication of the digit. It may take place in isolation, may be with autosomal dominant inheritance, or it may be part

of a genetic syndromes, for example: acrocallosal syndrome (with delay in development and corpus callosum abnormalities), Carpenter and Pfeiffer syndromes (with craniosynostosis), Fanconi and Diamond-Blackfan anemias, and Holt-Oram syndrome (with congenital heart diseases) ، Central polydactyly is a rare condition in which there is duplication of the ring, middle, index fingers. It may be accompanied with syndactyly and cleft hand. Most cases are syndromic, Postaxial polydactyly is the most common, it involves an extra digit on the ulnar side of the upper limb/ fibular side of the lower limb. The extra finger is rudimentary in most of cases, but in some cases its completely developed. In some cases this type of polydactyly is usually an isolated defect. While in others, it is more often associated with a syndrome containing multiple congenital anomalies or chromosomal abnormalities. examples of such syndromes: Greig cephalopolysyndactyly syndrome, Meckel syndrome, Ellis-van Creveld syndrome, Down syndrome, McKusick-Kaufman syndrome, and Bardet-Biedl syndrome.

Syndactyly: is webbing or fusion of digits (fingers or toes). Numerous types are known, and the majority follow an autosomal dominant inheritance pattern. In simple syndactyly there is just fusion of the soft tissue, while in complex syndactyly there is fusion of the bones. Complex syndactyly occurs in Apert syndrome (with craniosynostosis). Syndactyly of the ring and the small fingers is a common component of