


**Research Article**

## Exploratory Study of Risk Factors for Congenital Malformations in Morocco

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### Abstract

**Background:** The aim of the study is to describe the teratogenic risk factors of congenital malformations in a large sample from the Moroccan population.

**Methods:** It is a descriptive epidemiological study conducted between January 1<sup>st</sup>, 2011 and June 30<sup>th</sup>, 2016 at the "Les Orangers" maternity and reproductive health hospital in Rabat, Morocco.

The data were collected on pre-established sheets and on the hospital's malformations register.

**Results:** A total of 245 cases of congenital malformations were recorded out of a total of 43,923 births with a prevalence of 5.58 per thousand.

Women over 35 years represent 24.1% of all cases. Consanguinity was found in 22.4% of cases, maternal diabetes in 7%, Fenugreek and herbs intake in 28.6%, and medication in 2.8%. Almost all of women (97.5%) are of low to moderate socio-economic level. Antenatal diagnosis was performed in only 28.6% of cases.

**Conclusion:** Causes and risk factors of congenital malformations are diverse, which requires the application of large preventive and therapeutic approaches. However, the identification of risk factors specific to each country is necessary to establish specific preventive measures.

**Keywords:** Congenital malformation; Risk factors; Antenatal diagnosis; Prevention; Morocco

**Abbreviations:** CM: Congenital malformations; HIV: Human immunodeficiency virus; CMV: Cytomegalovirus; HMSRO: "Les Orangers" maternity and reproductive health hospital in Rabat; WA: weeks of amenorrhea; IUGR: Intrauterine Growth Restriction; FDIU: Fetal death in utero; SOGC: Society of Obstetricians and Gynecologists of Canada; NSAIDs: nonsteroidal anti-inflammatory drugs; ANSM: National Agency of Safety of the Drug and Health Products

### Background

Congenital malformations (CM) are a group of various prenatal disorders that might be caused by single gene abnormalities, chromosomal disorders, multiple heritable factors, environmental teratogens, or micronutrient deficiencies. In low and middle-income countries, some maternal infectious diseases, such as syphilis or rubella, are a major cause of congenital malformations. Furthermore, maternal diseases, such as diabetes, epilepsy, some particular medical conditions, such as iodine or folic acid deficiencies, exposure to drugs and recreational drugs, including alcohol and tobacco, and environmental chemicals and high dose radiation are other factors causing CM.

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**Citation:** K Forci, E Bouaiti, MH Alami, A Mdaghri Alaoui, A Thimou Izgua. Exploratory Study of Risk Factors for Congenital Malformations in Morocco. *Journal of Biotechnology and Biomedicine*. 6 (2023): 438-445.

**Received:** September 15, 2023

**Accepted:** September 22, 2023

**Published:** October 03, 2023

Despite the progress made in molecular biology and imaging, 50% of CM are of unknown etiology [1]. The causes of malformations in humans can be divided into three groups: [2]

#### Genetic causes:

- Chromosomal aberrations in 10-15%,
- Mendelian inheritance: 2-10%

#### Environmental causes:

- Maternal / placental infections (rubella, toxoplasmosis, syphilis, human immunodeficiency virus (HIV), cytomegalovirus (CMV), ...): 2-3%
- Maternal pathology (diabetes, phenylketonuria, ...): 6-8%
- Drugs and chemical agents (alcohol, androgen, Phenytoin, Thalidomide, 13 cis retinoic acid, ...): 1%
- Irradiation: 1%

**Multifactorial causes:** 20-25%

**Unknown causes:** 40-60%

In developing countries, CM are not a public health priority. In our country, routine antenatal screening for malformations is not widespread and there is still no national register of all CM cases. In addition, at the national level, no studies have been conducted to determine the prevalence of these anomalies neither their causes nor associated risk factors.

For that, the identification of CM causes and risk factors is necessary to adapt prevention strategies and to target the suspected factors.

The objective of our study is to describe the teratogenic risk factors of CM in the Moroccan population.

## Methods

### Study design

The study was run from January 1<sup>st</sup>, 2011 to June 30<sup>th</sup>, 2016 at the "Les Orangers" maternity and reproductive health hospital in Rabat (HMSRO). This hospital is a level 3 structure with an average of 8000 deliveries per year. This study included all pregnant women whose fetuses or newborns have one or more malformations detected by antenatal ultrasound and / or discovered on clinical examination at birth, regardless of the term or outcome of the pregnancy. Parents were informed about the terms and objectives of the study and their consent was obtained. Cases of refusal to participate in the survey were excluded as were the cases where the malformation was suspected on obstetrical ultrasound but was invalidated at birth. Thus, we define: [3]

**Live birth:** it is the expulsion or extraction, from the

mother's body, of a conception product weighing  $\geq 500$ grs (or  $\geq 22$  WA) which after this separation breathes, or has any other sign of life, such as heart beating, umbilical cord pulsation or effective contraction of a muscle subjected to the action of the will, whether the cord was cut or not.

**Fetal death:** spontaneous cessation of fetal cardiac activity at a gestational stage greater than 14 weeks of amenorrhea. It can occur before labor = antepartum fetal death or intra-uterine fetal death, or during labor = intrapartum fetal death or perpartum death.

**A premature newborn:** if born before 37 weeks of gestation.

**Full term newborn:** from 37 to less than 42 full weeks (259 to 293 days) of gestation.

**Intrauterine Growth Restriction (IUGR):** when the fetal birth weight is below the lower limit of the norm that is the 10th percentile of the reference curves.

### Data collection

After informing parents about the objectives of our study and obtaining their informed consent, one of the participating doctors collects data about:

- Socio-economic and biodemographic anamnestic parameters of mothers,
- Consanguinity,
- History of malformation in the family or siblings,
- Maternal serology,
- Characteristics of pregnancy and childbirth (follow-up, pregnancy, mode of delivery, term of delivery),
- The possible exposure to teratogenic products (taking drugs and plants or contact with toxic products, habitat close to an industrial factory ....) and the time of exposure during pregnancy.
- Newborn data.

Data were recorded by the doctor who examines the newborn in collaboration with the pediatrician, on pre-established sheets and on the malformations' register of the HMSRO.

### Statistical analysis

It is a descriptive epidemiological study. Data entry and statistical analysis were performed by SPSS 18.0 software. Qualitative variables were expressed in numbers and percentages, and quantitative variables in mean and standard deviation.

## Results

During the study period, 245 cases of CM were diagnosed

out of a total of 43,923 births. The total prevalence was 5.58 per thousand births (55.78 per 10,000 births).

### Sociodemographic and obstetrical characteristics of mothers:

The average gestationality was 2.39 with extremes of 1 to 8 and the average parity was 1.83 with extremes of 0 to 6. About 37.1% of women were primiparous, while 37.6% were pauciparous and 25.3% were multiparous.

Low socio-economic level was described in 70% of women. At the medical level, 73% of women have followed their pregnancy.

Rubella and toxoplasmosis immune status was unknown in half of women. Only one positive case of HIV and one case with positive syphilitic serology were identified.

Folic acid supplementation during pregnancy was noted in 27% of cases. Mean gestational age was  $36.80 \pm 5.11$  weeks of amenorrhea.

A medical termination of pregnancy was performed in 5.3% of cases. 70.6% of women gave birth naturally, and 29.4% delivered by caesarean section.

Fetal death in utero (FDIU) was reported in 19.2% of cases, while IUGR was described in 12.7% of cases. Preterm delivery and full term birth were noted in 13.1% and 73% of cases, respectively.

Prenatal diagnosis was performed in 28.6% of cases; of which 5.7% (4 cases) in the first trimester, 47% (33 cases) in the second trimester, and 48.5% (34 cases) in the third trimester. Whereas in more than two thirds of cases (71.4%) the diagnosis was made at birth during a systematic clinical examination of the newborn.

All the sociodemographic and obstetrical data of mothers are summarized in Table 1.

### Risk factors associated with congenital malformations

The mean age of mothers was  $30.38 \pm 6.88$  with extreme ages of 16 and 48 years. Women aged over 35 years represent 24.1% (59 women), of whom almost one third gave birth to newborns with Down syndrome. Consanguinity was noted in 22.4% of CM cases, of which 74.5% were related to first degree consanguinity. CM history was noted in the siblings and in the family in 5.7% and 4.5% of the cases, respectively. Moreover, complications during pregnancy including diabetes were noted in 7% of cases. Consumption of Fenugreek during pregnancy was noted in 46 cases (18.8%), of which 11 cases (24%) had neurological abnormalities such as anencephaly (63%), hydrocephalus (27%) and holoprosencephaly (10%). The intake of various plants was found in 9.8% of cases, while the drug intake was noted in 2.8% (Table: 2).

**Table 1:** Sociodemographic and obstetrical characteristics of malformed newborns' mothers at the HMSRO, Rabat, Morocco

	Number of cases	Percentage %
<b>Marital status</b>		
Married	241	98.4
Not married	4	1.6
<b>Profession</b>		
Housewife	229	93.5
Working mother	16	6.5
<b>Socio-economic level</b>		
Low	172	70.2
Middle	67	27.3
High	5	2
Unknown	1	0.4
<b>Medical history</b>		
Diabetes	8	3.3
Gestational Diabetes	9	3.7
Malformed foot	1	0.4
Malformed uterus	1	0.4
Epilepsy	1	0.4
Depressive disorders	1	0.4
Hypothyroidism	1	0.4
Family diabetes	41	16.7
<b>Gestational age</b>		
<22 WA	6	2.5
22-36 WA	59	24.5
≥37 WA	176	73
<b>Parity</b>		
Primiparous	91	37.1
Pauciparous	92	37.6
Multiparous	62	25.3
<b>Pregnancy follow-up</b>		
No follow-up	23	9.4
Well follow-up	179	73.1
Poor follow-up	43	17.6
<b>Prenatal diagnosis</b>		
Not done	175	71.4
Done	70	28.6
at T1	4	1.6
at T2	33	13.5
at T3	34	13.9
<b>Mode of delivery</b>		
Normal	173	70.6
Caesarean section	72	29.4
TIP	13	5.3
<b>Outcome of pregnancy</b>		

FDIU	47	19.2
TIP	13	5.3
IUGR	31	12.7
Early-term delivery	32	13.1
Full-term delivery	176	73

WA: weeks of amenorrhea, T: trimester, FDIU: Fetal death in-utero, TIP: Therapeutic interruption of pregnancy, IUGR: Intrauterine Growth Restriction

**Table 2:** Risk factors associated with CM in malformed newborns' mothers at the HMSRO, Rabat, Morocco

	Number of cases	Percentage %
<b>Age</b>		
<35years	186	75.9
≥35years	59	24.1
<b>Consanguinity</b>		
Absence	190	77.6
Presence	55	22.4
Degree 1	41	74.5
2	10	18.2
3	4	7.3
<b>Malformation history in siblings</b>	14	5.7
<b>Malformation history in family</b>	11	4.5
<b>Complications during pregnancy</b>	44	18
Diabetes	7	2.9
Gestational diabetes	10	4.1
Anemia	6	2.4
HIV	1	0.4
Hypothyroidism	1	0.4
Pemphigoid gestationis	1	0.4
Syphilis	1	0.4
<b>Fenugreek consumption</b>	46	18.8
T0	4	1.6
T1	35	14.3
T2	18	7.3
T3	25	10.2
<b>Other plants consumption</b>	24	9.8
T0	3	1.2
T1	19	7.8
T2	7	2.9
T3	6	2.4
<b>Medication</b>	7	2.8
Paracetamol	3	1.2
Acetylsalicylic acid	1	0.4
Corticoids	1	0.4

Aluviq+ Duovir (AZT)	1	0.4
Sodium Valproate	1	0.4
<b>Toxic habits</b>	0	

HIV: Human Immunodeficiency virus, T: trimester, T0: pre-conception period, AZT: Azidothymidin

## Discussion

Although in almost half of congenital anomalies no specific cause is established, still there is a number of well-known risk factors [4]. In our study, the rate of women over 35 years represents one quarter of cases. However, it has been reported in the literature that the risk of CM is higher after the age of 35 years. In general, as a literature review by Khoshnood reports, the prevalence of chromosomal and non-chromosomal abnormalities increases with maternal age [5]. This finding has contributed to the recommendation of routine prenatal screening in women over 35 years old. In the present study, we have recorded 35 cases of trisomy 21 cases, which correspond to 14.3% of all cases with CM. Half of Trisomy 21 cases were born to mothers over the age of 35 years. Indeed, advanced maternal age increases the risk of chromosomal abnormalities, particularly Down syndrome, as reported by Hook's study that shows a rate of 2 per 1000 for the lowest maternal ages, 2.6 for 1000 to 30 years, 5.6 for 1000 to 35 years, 15.8 for 1000 to 40 years and 53.7 for 1000 to 45 years [6]. Nevertheless, the risk of several CM exists even among young women. For this reason, in Canada, the Society of Obstetricians and Gynecologists of Canada (SOGC) recommends prenatal screening for fetal aneuploidy to all pregnant women regardless of age [7]. In our study the percentage of consanguinity is 22.4% of which three quarters (74.5%) of the cases are first degree. In fact, consanguinity increases the risk of heart, brain, and other genetic disorders [8]; it increases the prevalence of rare genetic congenital abnormalities by doubling the risk of newborn and infant death, intellectual disability, and other congenital anomalies when the parents are first cousins. Some ethnic communities, such as Ashkenazi Jews or Finns, have a relatively high prevalence of rare genetic mutations with an increased risk of CM. A UK survey conducted between 2007 and 2010 on 11,300 newborns in the city of Bradford that includes a large Pakistani community characterized by a high percentage of consanguineous marriages concluded that the risk of CM goes from 3% when parents are not related to 6% when parents are cousins [8]. In turkey, a study has reported a rate of 23.2% of consanguinity among parents of children with CM [9]. Family history of CM has been significantly associated with the risk of CM in several series such as Shawky's study, which reported a family history of CM in 16.69% of cases [10]. In our series, the rate was 10.2%. In 94% of cases, severe CM occur in low- and middle-income countries where the mothers are exposed to malnutrition and infectious agents

or teratogenic products that may induce abnormal prenatal development [4]. In our series, 97.5% of women are of low to moderate socio-economic status. Maternal infections such as syphilis, rubella, toxoplasmosis and cytomegalovirus and HIV infections are a major cause of CM in low- and middle-income countries.

### In the present study

- Rubella serology was performed in 47.7% of women of whom 26.9% were immunized.
- Toxoplasmosis serology was made in 51.8%, of which only 15.9% were immunized.
- Syphilitic serology was determined in 62% of cases with a single case of evolutionary infection found in the context of clubfoot.
- Hepatitis serology was only performed in 17.6% of cases for hepatitis B and 14% for hepatitis C.
- HIV serology was investigated in 12.6% and was positive in one case with Down syndrome.

Although the link between maternal infections and the occurrence of CM is confirmed, in our context, serology investigations are not systematically run due to the lack of prenatal and pre-conception consultations by women, which make our interpretation of the collected results very complicated. Also, it explains the unknown immune status of almost the half of our cases. It is well-known that nutritional deficiencies are related to certain congenital anomalies. For example, folate deficiency increases the risk of neural tube defects in the newborn, and excessive vitamin A intake may affect the normal development of the embryo or fetus. However, in our series, folic acid supplementation was noted in only 27% of cases. Overweight and unbalanced diabetes increase the risk of birth defects. Indeed, several studies based on patient registers or cohort studies have reported an increased risk of malformations in the context of diabetes. A literature review, conducted between 1990 and 2005, have analyzed the teratogenicity of diabetes during pregnancy, found that the risk of CM in diabetes was increased [11, 12]. In our study, diabetes was found in 7% of malformation cases, a rate that is similar to that reported in Egypt (7.28%) [10]. In our context, the intake of Fenugreek and plants during pregnancy was found in 28.6%. Fenugreek (*Trigonella foenum-graecum*) is a plant widely cultivated in the Mediterranean area, India and China. Its grains are commonly consumed for the management of diabetes and hypercholesterolemia. It is used as a spice in Indian (curry), African and Moroccan cuisine. A study conducted by Skalli from the Moroccan Center of Pharmacovigilance reported the occurrence of CM such as hydrocephalus and spina bifida after ingestion of fenugreek during pregnancy [13]. Another study in mice exposed to a high dose of fenugreek

seeds concluded that exposure to fenugreek is responsible for the appearance of microcephaly probably due to abnormal proliferation of neurons and glial cells with significant stunted growth and impaired motor performance [14]. Kassem and al. observed a significant reduction in fetal and placental weight at 20 days of gestation, suggesting an embryo-fetal toxicity [15]. Fenugreek extract causes intrauterine growth retardation and impairs brain development at the doses of 500 and 1000 mg/ kg per day [16]. Exposure to alcohol, tobacco or radiation during pregnancy increases the risk of having a fetus or newborn affected by CM. Working or living near or outside landfills, blast furnaces or mines is also a risk factor, especially if the mother is exposed to other environmental risk factors or suffers from nutritional deficiencies. A case-control study conducted in Rhône-Alpes between 2001 and 2003 confirmed the presence of a link between the risk of the urinary tract malformations and exposure to emissions from municipal mass burn incinerators and that this risk is increased for mothers exposed to dioxins above a certain threshold in early pregnancy [17]. In our context, no case of contact with teratogenic agents has been reported because the hypothesis of environmental pollution has not been explored. In our study, drug intake; including paracetamol, acetyl salicylic acid, corticosteroids, antiretrovirals and antiepileptics; was noted in 2.8%. Studies have shown that the use of acetyl salicylic acid at low doses of 50-150 mg/day in the prevention of preeclampsia is teratogenic in rodents, monkeys, dogs and cats. Also, it induces neural tube closure abnormalities, skeletal abnormalities and cleft palates. At the doses of 250 and 1000 mg / kg, miscarriage and FDIU are induced [18]. In humans, studies have shown that taking aspirin in the first trimester causes congenital heart defects [19] and gastroschisis [20, 21, 22]. However, epidemiological data did not show an association between taking aspirin in the first trimester and increasing the rate of CM [23]. At high dose during the 2<sup>nd</sup> trimester of pregnancy, aspirin may cause premature closure of the ductus arteriosus with pulmonary hypertension and renal effects and intracerebral fetal hemorrhage [24, 25, 26, 27]. In fact, all NSAIDs (non-steroidal anti-inflammatory drugs) can lead to cardiac and / or renal fetal and / or neonatal toxicity, sometimes irreversible or even fatal [28]. Regarding corticosteroids intake, case-control studies have shown an increased risk of cleft lip or labiopalatine and IUGR when taking corticosteroids orally [29]. In our study, a case of short limb was identified in a woman who had taken corticosteroids associated with acetyl salicylic acid as part of Pemphigoid gestationis treatment. Antiretrovirals were only taken by one case of HIV-positive mother put on treatment at the beginning of the pregnancy, which gave birth to a new born with Down syndrome. A preliminary analysis of an observational study of 426 neonates conducted in Botswana in 2018 raised the risk of neural tube closure abnormality in 4 of the neonates of mothers treated with a combination of antiretrovirals

with an incidence of 0.9% [30]. Other studies have shown an increased risk of congenital heart disease [31], skin and musculoskeletal abnormalities [32]. Paracetamol intake was noted in three cases in our series; a case of hydrocephalus, a case of myelomeningocele, and a clubfoot case. However, several studies have reported that Paracetamol exposure during pregnancy may result in developmental alterations both in the brain with behavioral disorders and hyperactivity, and autism spectrum symptoms and paracetamol for more than 4 weeks during the first and second trimesters of pregnancy may increase the frequency of cryptorchidism [33]. Sodium Valproate intake was reported by one mother who was followed for epilepsy and stopped her treatment at the beginning of the first trimester. The outcome of this pregnancy was marked by the occurrence of a chylothorax and the perpartum death of the newborn due to a severe respiratory distress. According to the latest French report by ANSM (national agency of safety of the drug and health products) published in April 2019, the risk of malformation in case of valproic acid intake is multiplied by 4-5 compared to the general population. Besides, it's associated with the risk of occurrence of neural tube closure, oral cleft, hypospadias, facial dysmorphism, craniosynostosis, cardiac, renal, urogenital and limb malformations, and polymalformative syndromes [34]. The existence of neurodevelopmental disorders (development quotient / intelligence quotient decrease, developmental delays, autistic spectrum disorders) in children exposed in utero to valproic acid has been established regardless of the term of pregnancy and the administered dose, and these disorders are extremely severe and can lead to educational and professional disabilities. Data also suggest an increase in attention deficit disorder and hyperactivity.

### Limitations of the study

It is a descriptive study carried out in a single center,

As in most of these studies, taking medication during pregnancy is not always specified.

Poorly structured antenatal surveillance makes information about supplementation (iron, vitamins), serology, and antenatal diagnosis unavailable.

In case of fetal death in utero, only X-rays and autopsy can inform about the malformation etiology.

In order to notify all abnormalities including functional abnormalities, it is necessary to make a long-term follow-up, which was not the case in the present study.

### Conclusion

Our study raises more problems than solutions; among which:

- Lack of awareness of pregnant women during pregnancy,
- Low rate of CM cases that are diagnosed prenatally, consequently, setting up a strategy for CM antenatal screening is needed.
- The problem of CM national register that must be established,
- Lack of coordination with the Pharmacovigilance Center, hence the importance of creating a teratovigilance network able to communicate all statistical data permanently.

As a result, a systematized policy in the context of CM must be urgently implemented.

### Declarations

#### Ethics approval and consent to participate

The Ethical Committee of Biomedical Research, Faculty of Medicine and Pharmacy – Rabat, approved the study. Oral consent to participate was obtained from the parents.

#### Consent for publication

The consent for publication was obtained from the parents.

#### Data availability

Data are available upon reasonable request to the first co-author

#### Competing interests

All the authors declare that they have no competing interests

#### Funding

Not applicable

#### Authors' contributions

ATI was responsible for the study concept and design. KF coordinated the study and interviewed the parents. KF and EB analyzed the data. KF led the drafting of this manuscript, with input from all authors. ATI and MHA supervised analysis of the data and contributed to the writing. ATI, MHA, EB and AMA contributed to revision and final approval of the manuscript.

All the authors have approved the present version of the manuscript.

#### Acknowledgments

We would like to thank everyone who had contributed in this study.

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