

# Is There a Relationship between COVID-19 Infection and the Occurrence of Anencephaly? Observation of the Maternity of Mohammed the VI University Hospital of Marrakech

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## Abstract

**Introduction:** Morocco has experienced, like the whole world, the COVID-19 pandemic. Until the writing of this article, a subjective observation of the increase in the number of anencephaly has been observed in our facility. And since the teratogenic potential of the SARS Cov 2 virus is not sufficiently documented, we wondered if there would be a relationship between the relatively high number of anencephalic fetuses and COVID-19 infection. **Aim:** the objective of the study is to look for a possible correlation between the period of conception of these anencephalies and the pandemic. **Material and methods:** This is a retrospective study (from June 1, 2020 to May 31, 2022 in the Obstetrics Gynecology department, Faculty of Medicine and Pharmacy, CADI AYYAD UNIVERSITY Marrakech Morocco) consisting of the analysis of the number of patients in the target embryonic period (namely the closure of the neural tube: D18 to D30 of embryonic life) compared to the reference curves of the evolution of the SARS Cov2 pandemic. **Results:** The analysis of the number of patients at the target embryonic phase shows that many of our anencephalons (63%) were conceived during periods of high diffusion of the SARS Cov 2 virus in Morocco. **Conclusion:** Our study suggests a relationship between the COVID-19 pandemic and the occurrence of anencephaly, we cannot, however, highlight the type of direct or indirect relationship that binds them. Therefore, further studies should be considered to better investigate this relationship.

## Keywords

Anencephaly, Closure Neural Tube Anomaly, COVID-19, SARS Cov2,

## 1. Introduction

Anencephaly is a birth defect of the central nervous system that results from the absence of normal closure of the neural tube at the anterior end, usually between the 18th and 30th day of embryonic life. The fetus with this malformation lacks a forebrain and therefore has neither the ability to think nor coordinate. Its prevalence at birth would be between 1 case per 5000 and 1 case per 2000 [1]. A subjective observation of the increase in the number of anencephalies in the maternity hospital of the Marrakech University Hospital during the COVID-19 pandemic motivated us to consult the birth register. And since the teratogenic potential of the SARS Cov 2 virus is not sufficiently documented, it has been questioned whether there would be a relationship between the relatively high number of fetuses with anencephaly with the COVID-19 pandemic.

## 2. Objective

The objective of our work is to study the relationship between COVID-19 infection and the occurrence of anencephaly since the literature is poor on this issue.

## 3. Material and Method

This is a retrospective study between June 1, 2020 and May 31, 2022.

### 3.1. Methodology

The work consisted in collecting the records of patients in whom the diagnosis of anencephaly was made during this period. Due to the fact that the files may be incomplete concerning the anamnesis of the COVID-19 infection. The women concerned were recontacted and summoned in order to complete the anamnestic data. An exploitation sheet was established for this purpose, including the identity, the traditional risk factors, the circumstance of discovery, the clinical and paraclinical information, the infectious anamnesis of the woman and that of her spouse. The gestational age made it possible to know the date of conception as well as the target embryonic period (the closure of the neural tube which occurs between D18 and D30 of embryonic life), two fundamental data of our study. For each patient, we will look for a possible episode of COVID-19 infection and its distance in time from the target embryonic phase. For the entire sample, a comparison between the number of women in the target embryonic period and the epidemiological situation in Morocco [1] [2].

### 3.2. Integration Criteria

Any patient who gave birth during this period at the maternity hospital of the CHU Mohammed VI in Marrakech with the diagnosis of anencephaly, without

taking into account any associated malformations, the presence or absence of cardiac activity and/or the reason for consultation.

### 3.3. Exclusion Criteria

Any patient who gave birth during this period but whose presumed date of conception as well as the target embryonic phase will be prior to the appearance of the 1st case of COVID-19 in Morocco (*i.e.* March 22, 2020).

Any woman who has been diagnosed with anencephaly but has not given birth in our training.

The recruitment process made it possible to select 50 files. However, only 47 patients were eligible for our study.

### 3.4. Selection Bias

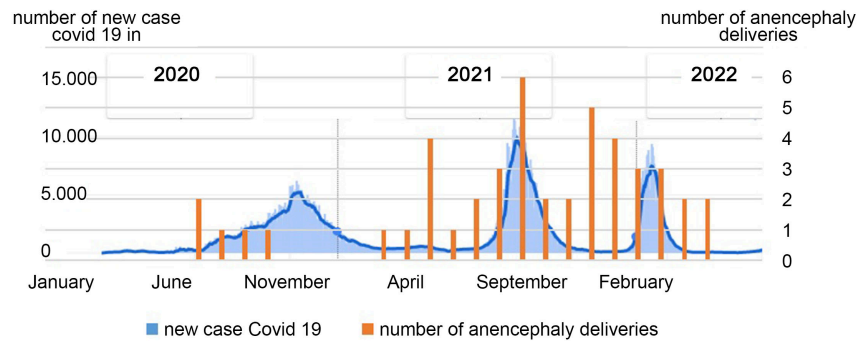
It should be noted that the obstetrics gynecology department of the Marrakech University Hospital receives all malformations because the only one in the region authorized to take care of them. Nevertheless, it happens that patients can give birth in other structures (lower level or in the liberal sector).

## 4. Results

### 4.1. Epidemiological Data

The frequency of deliveries is heterogeneous, with an average of 2.8 deliveries per month over the past 15 months. During the pandemic, we identified 47 parturients in whom anencephaly was diagnosed during an antenatal ultrasound in the gynecology and obstetrics department of the CHU Mohammed VI in Marrakech, an average of 23.5 deliveries per year (**Figure 1**).

The average maternal age of anencephaly at the time of diagnosis is 27.28 years with a maximum of 44 years and a minimum of 19 years. The average paternal age of anencephaly at the time of diagnosis is 37.67 years with a maximum of 52 years and a minimum of 24 years. Concerning the profession, 41 women (91%) out of 47 are without profession (housewife) the remaining professions are agricultural sector in one case (2.22%), hotel industry in one case (2.22%), service sector two cases (4.44%). Concerning the profession of the spouses, twenty-two of the spouses were unemployed, seven in the construction industry, five in the agricultural sector, five in the transport and logistics sector, four in the liberal trade sector and two in the construction sector. The hotel industry, concerning the geographical origin of parturients: 40 were from the regions of Marrakech, four from the region of Agadir and three from the region of Essaouira. Twenty-six (58%) women lived in urban areas compared to 19 (42%) in rural areas. Forty-four (93%) of the pairs were non-consanguineous versus 3 (7%) consanguineous. Seven women had a history of miscarriage, 4 women had a history of neonatal death, 2 women had a history of fetal death in utero and 2 women had a malformation syndrome as a history, both explained by consanguinity. A notion of taking fenugreek was found in 37 patients or 82.22% and a



**Figure 1.** Graph showing the evolution of the number of anencephaly deliveries compared to the curves of new cases of COVID-19 in Morocco.

notion of taking unknown plants in 5 patients or 11.11%. Not all women knew about the harmful effects of these herbs.

#### 4.2. Circumstance of Discovery

The circumstances of discovery are dominated by urgency in 24 cases (51%). The etiologies are: Threat of premature delivery in 9 cases (19%) of cases, Premature rupture of membranes in 5 cases (11%), Threat of premature delivery associated with Premature rupture of membranes in 2 cases (4%), patient in labor at term in 5 cases (11%), overterm in 2 cases (4%) and thrombocytopenia at term in 1 case (2%). The remaining 23 (49%) cases were diagnosed during routine prenatal ultrasound.

#### 4.3. Infectious History and Vaccination

Five women in the study had reported the notion of fever, 3 of them had reported the notion of flu syndrome, one of them had reported the notion of confirmed contact case. None of the women reported any notion of cough or dyspnoea. The women with a positive infectious anamnesis questioned had all located this episode in the 1st trimester. None of the women in the sample received a diagnostic test to confirm COVID-19 infection. None of the women had been vaccinated against the SARS COV2 virus. Three of the spouses in the sample had reported a notion of fever with chills and cough. The said episodes are concomitant with those of their wives. None of the men had a diagnostic test for COVID-19. Only 2 men in the study were vaccinated. The 2 men benefited from the vaccination respectively at 3 months and 2 months before the intercourse of fertilization.

#### 4.4. Clinical Data and Ultrasound

The average gestational age at the time of diagnosis was 30SA+1 days with an interval between 14SA+1 and 42SA+2. On ultrasound, the other associated malformations found are respectively: Deformity of the spine + clubfoot in 1 case, Spina bifida in 3 cases, Laparoschisis in 1 case and Cardiomegaly with single ventricle + cleft lip + pulmonary aplasia in 1 case. A fundic placenta was found in 100% of cases with a velamentous insertion of the cord in 1 case. Ultrasound

found 15 cases with fluid in normal quantity (32%), 30 cases with Hydramnios (64%) and 2 with oligo-anamnios (4%).

#### 4.5. Evolution of the Number of Patients in the Embryonic Phase

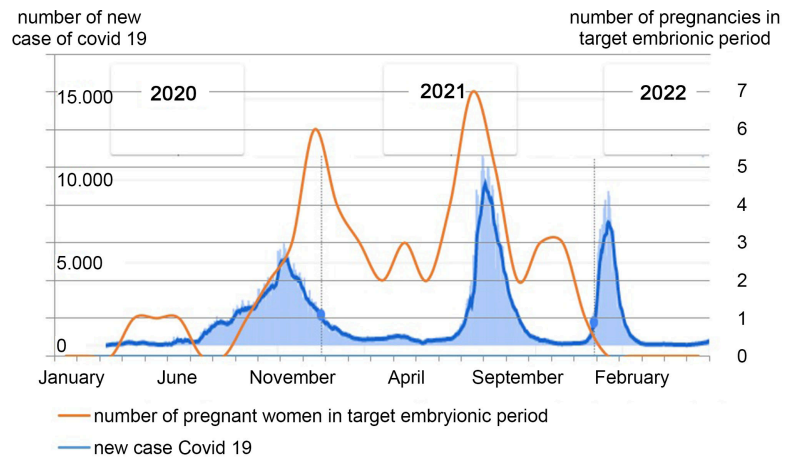
By counting the number of patients at the target embryonic phase (D18-D30 of embryonic life), we note the individualization of 2 peaks having their peak respectively in January 2021 and July 2021. Each of them followed by a drop then a slight elevation (**Figure 2**). It should be noted that many of the anencephalic patients were in the period of neural tube closure at the time of the strong spread of the virus in the Moroccan population: the 2 peaks observed total 30 patients (63.82%) including 16 (34%) during the first peak and 14 (29.98%) during the 2nd peak. Another interesting fact is that the duration of the peaks is consistent with the different waves of COVID-19 infection with a parallel evolution between the 2 curves.

### 5. Discussion

#### 5.1. General

Regarding maternal age, our results are consistent with those of the literature. With regard to diabetes, we know that the glycemic figure is correlated with the risk of malformation [3]. Multiparous women are more likely to contract COVID-19 because the virus circulates better and asymptotically in the pediatric population [4]. In our series, we find 51% multiparity and 49% primiparity. **Table 1** shows a comparison of the different results [5] [6] [7].

Fenugreek (*Trigonella foenum-graecum* L.), is an annual herbaceous plant of Mediterranean origin. Although widely used in phytotherapy, little scientific data attests to its therapeutic virtue. Skalli reported eight cases of malformations (hydrocephalus and spina bifida) coinciding with the ingestion of fenugreek seeds during pregnancy [8]. In our sample, 37 women (82.22%) consumed fenugreek against 8 women (11%) in Radouani *et al.* [1]. There is a notion of taking plants unknown in 5 patients or 11.11%. All these women were completely unaware of the risks incurred by consuming them during pregnancy. It is estimated that half of birth defects are preventable if women of childbearing age eat sufficient amounts of foods rich or fortified with folic acid. The recommended dose is around 0.4 mg to 0.8 mg/day of folic acid to reduce cases of anencephaly. It should be noted that this prevention is not absolute, but leads to a real and significant reduction in the risk of these severe malformations which are anomalies of closure of the neural tube [9]. None of the women in the sample studied received folic acid supplementation. Our results agree with those of the literature. The average gestational age of the sample studied is high compared to the other series, which supports the hypothesis of a delay in diagnosis and reduced access to health services during successive deliveries. Most authors agree on the high frequency of polyhydramnios in this case, our results are consistent with those of the literature. The presence of associated malformations is not rare, our results are in agreement with those of the literature (**Table 2**).



**Figure 2.** Graph comparing the evolution of the number of patients in our series in the target embryonic period and the COVID-19 pandemic.

**Table 1.** Table indicating the maternal age and the percentage of diabetes of the various series.

Authors	Number of cases	Age (range)	Diabetes %
<i>N. Obeidi et al. [3]</i>	26	30 (17 - 41)	3.8%
<i>Panduranga et al. [5]</i>	41	23 (19 - 28)	-
<i>Shilpa et al. [6]</i>	60	24.4 (20 - 40)	5%
<i>Ekmekci et al. [7]</i>	28	27 (17 - 46)	0%
<i>Our series</i>	47	27.28 (19 - 44)	8.51%

**Table 2.** Comparison of the age of pregnancy and the percentage of associated malformations between different authors.

Authors	Pregnancy Age (Range)	Number of cases with associated malformations (%)
<i>Panduranga et al. [5]</i>	21 weeks (16 - 34)	30/41 (73%)
<i>Shilpa et al. [6]</i>	22 weeks (20 - 30)	42/60 (70%)
<i>Ekmeksi et al. [8]</i>	18 weeks (13 - 32)	-
<i>Tan et al. [10]</i>	-	25/267 (9.4%)
<i>Ravikiran Ashok Gole et al. [11]</i>	-	16/20 (80%)
<i>Our series</i>	30 weeks + 1 (14 - 42)	6/47 (12.76%)

## 5.2. Epidemiology

The prevalence of anencephaly shows great variation over time and space. It is 1 per 1000 in France [12], 12 per 10,000 in Iran, 10.4 per 10,000 in China, 0.01 to 7.42 per 10,000 in Rijeka in Croatia, 1.49/1000 in Santos Dumout [13], 0.5 to 0.6 per 1000 in Singapore [14] and 0.5 to 6.5 per 1000 in India. In Morocco, the prevalence was about 10 cases per 10,000 births each year before the pandemic, figures that date from before the pandemic [1]. The annual prevalence of the sample studied is approximately 13.82 per 10,000 births. However, this is not the

first time that high prevalences have been recorded. A 2013 Indian study found a very high prevalence of 21 cases/10,000 births [15]. High numbers have been observed almost everywhere, especially in Tigray in Ethiopia, and suggest that this is a global phenomenon [16]. The preventive introduction of folic acid breaks the growth curve but does not stop it [17]: it reduces the occurrence of anencephaly by 20% [18].

### 5.3. The Different Embryonic Phases in Relation to the Pandemic

The analysis of the number of patients in the target embryonic period (D18-D30 of embryonic life) shows that many of our anencephalons (63.82%) were in the period of neural tube closure during periods of high circulation of the SARS Cov 2 virus in the Moroccan population. Therefore, we can legitimately suspect a direct or indirect link with the virus.

### 5.4. Infectious History

#### 5.4.1. Maternal Infectious History

Transplacental transmission of COVID-19 is possible but rare [19]. Apart from rare reported cases of fetal death in utero due to COVID-19 [20], COVID-19 positive pregnant women are 3 times more likely to be hospitalized in the intensive care unit, 2.9 times more likely to undergo invasive ventilation, 1.9 times more likely to die, but the risk of malformation remains about the same [21]. The disease has a similar spectrum of symptoms in pregnant and non-pregnant women. Although most symptoms are less common during pregnancy, they are still more likely to require admission to intensive care than non-pregnant women of childbearing age. An American meta-analysis had found that pregnant women with an active COVID 19 infection are more likely to have serious forms of multiple pathologies and more particularly those with vascular components [22]. The risk of fetal injury is correlated with the severity of maternal COVID-19 infection [23]. Vaccination against COVID-19 does not a priori present any danger to the maternal and/or fetal prognosis. Vaccination should be encouraged taking into account the benefit/risk ratio [24]. The various vaccines in circulation do not show any notable differences either in terms of efficacy or in terms of complications [25]. As the main result of our study 93% of the sample did not have any infectious event related to COVID-19.

#### 5.4.2. Paternal Infectious Anamnesis

The oxidative stress can be possibly be caused by COVID-19, could reduce sperm motility and increase sperm DNA fragmentation [26] [27]. Spermograms carried out respectively between 56 and 109 days [28] and 37 - 52 days [29] do not find any significant abnormality. Overall, these preliminary data suggest that mild disease does not appear to have a negative effect on spermatogenesis. However, given the nature of the sample, the small sample size and the lack of long-term follow-up, it is imperative that further studies be carried out. We found 3 spouses in our study who had reported a notion of fever with chills and

cough. The said episodes are concomitant with those of their wives. None of the men had a diagnostic test for COVID-19. Only 2 men in our study were vaccinated. The 2 men benefited from the vaccination respectively at 3 months and 2 months before the sexual intercourse of fertilization. If SARS Cov2 seems to have a tropism for the human testicle, especially the Leydig and Sertolli cell, the infectious episode of the spouses at the time of the target embryonic phase is of no value. Because the testicular lesions capable of sufficiently corrupting the genetic material of the spermatozoa must be localized well before the fertilizing intercourse [26] [27].

#### **5.4.3. Hypotheses on the Physiopathological Mechanism**

The literature is very poor regarding the relationship between COVID-19 infection and anencephaly. This is one of the main motivations for this study. However, all the studies converge on the fact that the virus presents a negligible teratogenic risk [27] Giampreti *et al.* [30] found no significant increase in the risk of malformation occurring either by the virus or by the various molecules used in his treatment. The origin of anencephaly is multifactorial, with interaction of environmental factors (consumption of fenugreek, deficiency in folic acid and vitamin B12 during the periconceptual period [31] [32] and genetics [33]. However, the pathogenesis still remains obscure and controversial. Regarding the COVID-19 infection, co-expression of the ACE2 and TMPRSS2 genes is required for infection to occur, as SARS-CoV-2 uses the ACE2 receptor for entry and the serine protease TMPRSS2 for protein S initiation. 19. The vertical route of transmission (transplacental in utero, mother-newborn contact during childbirth or breastfeeding) is possible. ACE2 receptors required for viral infection are expressed in the placenta, ovaries, uterus and vagina and may be involved in vertical transmission. mother-newborn contact during childbirth or breastfeeding) is possible. It is true that the risk of vertical transmission is very rare but not zero. This does not exclude the hypothesis of contamination during embryonic life since the Trophectoderm has ACE2 receptors necessary for the binding of the Spike protein of SARS Cov 2. Their concentration varies between 3% and 69% [25]. A concentration of at least 1% is sufficient for a cell to be a target of the virus [25].

#### **5.5. The Results of the Study**

The main result that emerges from this study and that the increase in the number of cases of COVID-19 goes in parallel with the number of anencephalons in the study. It should be noted that the obstetrics gynecology department of the Marrakech University Hospital receives all malformations because the only one in the region authorized to take care of them. In view of all these results, two hypotheses emerge:

- 1) The first is that a direct physiopathological mechanism favors the occurrence of anencephaly.
- 2) The second is that the mechanism of association is indirect and rests on a



social and economic basis: the pandemic having precipitated several households into precariousness, consequently leading to a reduction in their quality of life. these households can no longer bear the costs of medical care, no longer have access to information (not all the women interviewed suspect the effects of fenugreek) and may even turn to riskier alternatives, in particular traditional medicine.

### 5.6. The Limitations of the Study

Unfortunately, the study comes up against several limitations: It is an observational and non-comparative study, so the relative risk cannot be determined. It is also subject to several biases: in particular memorization bias (some women were questioned about facts dating back several months) and selection bias (some women having simply given birth in another hospital structure).

However, the study has the merit of pointing the finger at an unsuspected relationship and clearly shows that there is a certain relationship between the COVID-19 pandemic and the occurrence of anencephaly. The mechanism of this relationship is not completely elucidated but could encourage more daring studies.

## 6. Conclusion

In the opposite of the data in the literature which stipulates that the Sars Cov 2 virus has a minimal teratogenic risk [27] [28] [29] [30]. Our study has the merit of being a pioneer in examining the relationship between the COVID-19 pandemic and the occurrence of anencephaly. The results are in favor of the existence of this relationship without providing a clear answer on why and how. Whatever the answer, more focused studies need to be conducted, including prospective randomized clinical trials.

## Disclaimer

The data in this document were collected after informed consent of the couples participating in this study.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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