Long-term infant outcomes after hyperbaric oxygen treatment for acute carbon monoxide poisoning during pregnancy

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Fetal development; Hyperbaric medicine; Long-term adverse effects; Pregnancy outcome; Pregnancy trimesters

Abstract
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Introduction: Carbon monoxide (CO) poisoning in pregnant women is linked to foetal mortality of 36–67%. This study assessed long-term fetal outcomes following hyperbaric oxygen treatment (HBOT) for acute CO poisoning in pregnant women. The effects of clinical severity parameters and pregnancy trimester were also analysed.
Methods: A retrospective review of 28 pregnant patients who received HBOT for acute CO poisoning between January 2013–June 2016 was made. Adverse events, birth week, birth weight-height, birth complications, and the age of crawling, walking independently, talking (first words) of their children were recorded.
Results: Twenty-eight singleton pregnancies were included. One fetus was dead before HBOT. Three adverse events were reported: abortion, premature birth, and limb malformation. All remaining patients (n = 24) delivered healthy term infants and reported normal neurophysiological development. At final interview the median age of babies was 34 (8–44) months and none had any diagnosed disease. There was no relationship between clinical severity parameters and long-term outcomes. However, the pregnancy trimester at the time of CO poisoning had a significant relationship to birth weight (P = 0.029). Also, the week of pregnancy at the time of the incident correlated with the age of walking independently (P = 0.043, r = 0.436).
Conclusions: This is the largest relevant series and longest follow-up to date. Adverse outcomes were likely incidental because the mothers' medical histories revealed alternative aetiologies. There was no definite evidence of fetal morbidity or mortality after HBOT in this study. HBOT may improve long-term fetal outcomes after in-utero CO poisoning without complications.

Introduction

Carbon monoxide (CO) poisoning is responsible for more than 20,000 emergency department (ED) admissions annually in the USA.[1] Pregnant patients are estimated to make up 4.6% to 8.5% of these cases.[2,3] Unfortunately, the resulting fetal mortality rate is between 36% and 67%, while the maternal mortality rate is between 19% and 24%.[4,5] Even for experienced practitioners, CO poisoning can be misdiagnosed easily due to its non-specific symptoms, which may lead to improper treatment and increase the degree of fetal morbidity and mortality.

The fetus is particularly susceptible to CO poisoning. Firstly, fetal haemoglobin has higher affinity for CO compared to maternal haemoglobin. Secondly, fetuses have a more prolonged CO elimination period than adults since they cannot increase their tidal volume or ventilation rate.[6] Outcomes resulting from CO poisoning depend upon the stages of gestation during poisoning, the severity of maternal CO exposure and the chronicity of exposure.[7,8] While exposure earlier in gestation might result in anatomical malformation, later exposures are expected to be related to neurological sequelae due to hypoxia.[7] Preterm delivery, hypoxic-ischaemic encephalopathy, hypotonia, cerebral palsy, areflexia, persistent seizures, microcephaly, cardiomegaly, limb malformations, fetal growth retardation, intrauterine fetal death, and even sudden infant death are reported to be associated with CO poisoning.[6,7]

Initial treatment for CO poisoning includes normobaric oxygen treatment (NBOT);[7,8] the effectiveness of NBOT for an affected fetus is difficult to ascertain as there is no diagnostic method available to detect the severity of fetal exposure accurately.[3] It has been reported that the fetus needs five-times longer than the mother's oxygen treatment period.[7,8] Hyperbaric oxygen treatment (HBOT) provides a higher partial pressure of oxygen in the blood, accelerates the CO release from haemoglobin and reduces neutrophil adhesion to the endothelium, so should be of greater benefit than NBOT.[9] However, gross congenital malformations, retrolental fibroplasia, retinal detachment, microphthalmia,

stillbirth, neonatal death, and premature birth were reported in animals exposed to maternal hyperoxia in the 1960s, leading to safety concerns.[10,11] However, there are no studies reporting any adverse effects on human fetuses exposed to HBOT, to the author's knowledge.[7,8] Acute CO poisoning in a pregnant woman is an accepted indication for HBOT according to the Undersea and Hyperbaric Medicine Society (UHMS).[8,9] Nevertheless in several countries, HBOT is still not recommended for pregnant patients except for life-threatening conditions. Evidence on fetal adverse effects of HBOT is lacking.[12] This subject is difficult to investigate, as it is not ethical to conduct randomised controlled prospective human studies to research fetal adverse events. However, clinicians still have two major unanswered questions in this field: the physiological (or pathophysiological) effects on the fetus during HBOT and whether HBOT is effective in preventing CO-related complications in fetuses.

The limited number of HBOT centres and lack of diagnostic methods for use in fetuses have resulted in a paucity of research on fetal outcomes after CO poisoning, with the existing literature being composed mainly of case reports. Long-term follow-up of surviving infants may shed light on the benefits and complications of HBOT; there are only two long-term follow-up studies published in English to date.[8,13]

The present study analysed the long-term outcomes for fetuses treated with HBOT after acute in-utero CO poisoning. Outcomes were classified into three main periods: pregnancy, birth, and after birth. In the first instance, the aim was to determine the undesired fetal outcomes that were associated with CO poisoning or were found to be coincidental. Secondly, the aim was to determine the undesired fetal outcomes associated with HBOT. Finally, an anlysis was undertaken on the effects of clinical severity parameters and pregnancy trimester during the poisoning on long-term fetal outcomes.

Methods

The study was approved by the Ethical Committee of our institution (Approval number 2020/85, date 25/02/2020).

This was a retrospective review of the records of pregnant patients who received HBOT for acute CO poisoning between 01 January 2013, and 01 June 2016. HBOT was carried out in either a monoplace or multiplace chamber at the same single institution which is a regional referral centre for HBOT. Patients may be transported to the centre from other hospitals and from other surrounding cities. The monoplace chamber protocol involved breathing 100% oxygen at 202.6 kPa for 75 minutes (10 minutes compression, 10 minutes decompression) or breathing 100% oxygen via a mask at 243.1 kPa for 90 minutes with a 5-minute air break (15 minutes compression, 15 minutes decompression). The multiplace chamber protocol involved breathing 100% oxygen at 243.1 kPa for three 30-minute periods with 5-minute air breaks (15 minutes compression, 15 minutes decompression). Additional sessions were given daily until maternal symptoms were fully resolved, as assessed by a hyperbaric medicine specialist.

Table 1
Severity grading for CO poisoning[13]

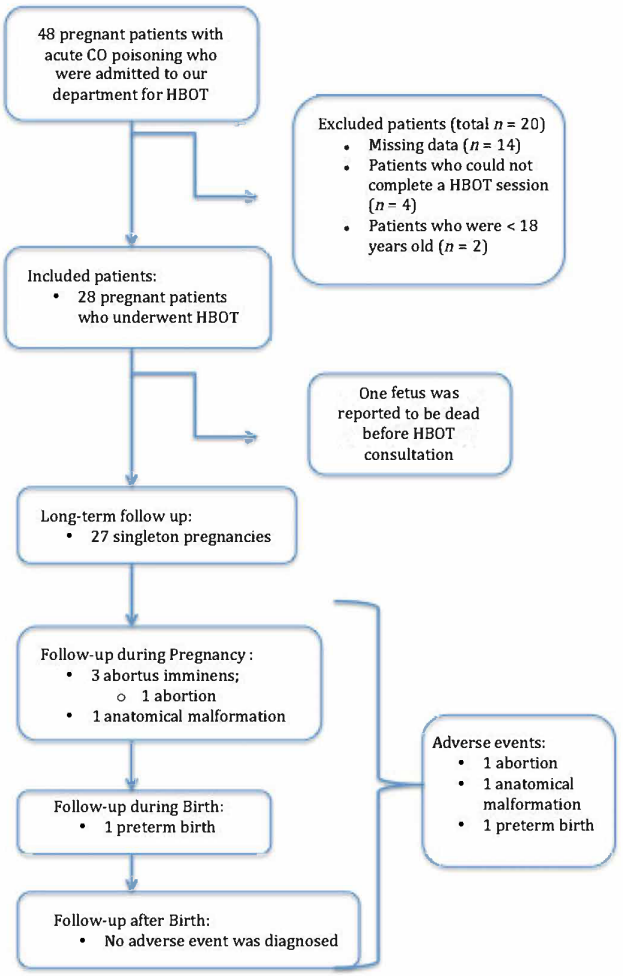
Severity	Symptoms
Grade 0	No symptoms
Grade 1	Alert, oriented
Grade 2	Alert, mental state alterations
Grade 3	Not alert, disorientation
Grade 4	Disorientated, depressed sensorium
Grade 5	Comatose

The carboxyhaemoglobin (COHb), white blood cell (WBC) count, blood pH and lactate level at the time of ED admission, electrocardiogram (ECG), symptoms, week of pregnancy, obstetrician consultation, medical history and the time elapsed before HBOT were reviewed from departmental records. Pregnancy problems after HBOT, birth week, birth weight and height, birth-related problems, age of crawling, walking independently and talking (first words), and the health status of infants were analysed as long-term follow-up parameters from patient records made during telephone interviews with parents. Exclusion criteria were: mother's age < 18 years old; inability to complete one HBOT session; and missing long-term follow-up data.

Clinical severity was classified according a previously published system (Table 1).[13] Additionally, transient/prolonged unconsciousness, cardiac abnormality, COHb level, and HBOT delay were determined as clinical severity parameters. These parameters and pregnancy trimester were compared with long-term infant outcomes (birth week, birth weight, birth height, crawling, walking independently and talking [first words] age). The COHb subgroup cut-off was determined to be 25%, according to the UHMS HBOT indication criteria for acute CO intoxication.[9] The time elapsed before HBOT was divided into two groups, ≤ 6 h and > 6 h delay, for statistical analyses. This cut-off was adopted from studies suggesting that the optimal time for HBOT is as soon as possible, preferably within the first six hours following CO exposure.[14,15]

Data analysis was performed using SPSS Statistics Version 21 (IBM Corp., Armonk NY, USA). The data were reported as *n* (%) and mean (standard deviation). Non-normal data were reported as median (range). The Shapiro-Wilk test was performed to determine the normal distribution of continuous variables. Pearson or Spearman correlation analysis was performed to analyse the linear correlation between variables. The relationship between pregnancy trimester and long-term outcome parameters was analysed with the Kruskal-Wallis test. Further binary comparisons were completed using the Mann-Whitney U test. Chi-square or Fisher's exact test were used for analysis of the

Figure 1
Flow chart of follow-up period and patient selection regimen



comparisons between pregnancy trimester and discrete variables of long-term outcome. The relationship between clinical severity groups, COHb groups, HBOT delay groups, transient/prolonged unconsciousness groups, cardiac abnormality groups, and long-term outcome parameters was analysed by Mann-Whitney U for continuous variables and by Chi-Square or Fisher's exact test for discrete variables. $P < 0.05$ was considered statistically significant.

Results

Forty-eight pregnant patients with acute CO poisoning were admitted to our department for HBOT. Patient selection and follow-up processes are reported in Figure 1. Twenty-eight pregnant patients were included in the present study. The demographic data of the patients during CO poisoning are shown in Table 2. Only one fetus whose mother had presented with Grade 5 severity was reported dead before HBOT consultation. All the remaining patients (n = 27, 96.4%) had reported a normal obstetric examination before HBOT. However, the obstetric consultation report included only whether the fetal heart beat was present or not. Patients' clinical severity and pregnancy trimesters are presented in

Table 2
Demographic and biochemical data of the 27 analysed patients following the CO poisoning incident; CO – carbon monoxide; COHb – carboxyhaemoglobin; HBOT – hyperbaric oxygen treatment; WBC – white blood cells. Note: percentages are calculated on a small sample size

Parameter	Mean (SD) or median [range] or *n* (%)
Age (years)	26.8 (4.9)
Pregnancy week	18 (8.5)
COHb (%)	27.9 [15.6–55.2]
WBC (10^3 cells·uL^{-1})	12,318 (6,602)
pH	7.40 (0.05)
Lactate (mmol·L^{-1})	2.92 (3.03)
HBOT delay (hours)	4 [2–13]
CO source	
Stove	12 (42.9%)
Natural gas	9 (32.1%)
Water heater	6 (21.4%)
Other	1 (3.6%)
Clinical severity grade[13]	
Grade 0	3 (10.7%)
Grade 1	13 (46.4%)
Grade 2	8 (28.6%)
Grade 3	3 (10.7%)
Grade 4	0 (0%)
Grade 5	1 (3.6%)

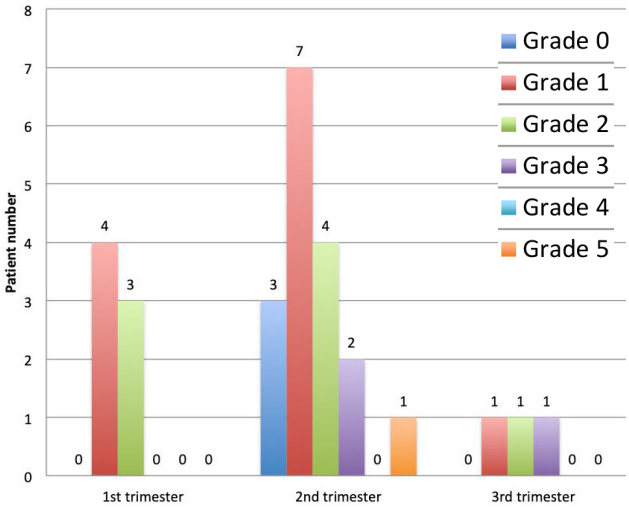
Figure 2. Only one patient's pregnancy trimester information was missing. The median completed HBOT treatment number was 1 (1-2). Twenty-five patients underwent one HBOT treatment, and three patients underwent two HBOT treatments.

The long-term follow-up data were analysed in 27 surviving patients due to one fetus's death before HBOT (Figure 1). Three cases (11.1%) had an abnormal outcome including: abortion (n = 1), premature birth (n = 1), and anatomical malformation (n = 1). Twenty-four of the 27 patients (88.9%) delivered full-term healthy infants with normal birth weight. Six patients (21.4%) continued to smoke during their entire pregnancy. None of the patients reported drinking alcohol during pregnancy.

FOLLOW-UP DURING PREGNANCY AFTER HBOT

Four patients (14.3%) had an abnormal obstetric follow-up, with three patients reported having *abortus imminens*. Only one of these resulted in medical abortion, due to preterm premature rupture of membranes two weeks after the poisoning. This patient (31-years-old, G3P1) had CO poisoning at 16 weeks of gestation with Grade 1 severity. She reported having vaginal bleeding problems for two weeks prior to the HBOT, which also continued afterwards. The

Figure 2
Number of patients by clinical severity (Table 1) and trimester



remaining two patients delivered healthy infants with normal birth weights at 39 weeks of gestation via spontaneous vaginal birth.

One patient (19-years-old, G2P1) who was poisoned at the 11th week of pregnancy had Grade 2 clinical severity. The obstetrician consultation was reported as normal before HBOT, and her headache was fully resolved after one HBOT session. However, a lower extremity malformation of the fetus was diagnosed at the sixth month of pregnancy with ultrasonography. The patient had a spontaneous vaginal delivery at full-term without any complication. At the follow-up interview, the parents stated that the baby had undergone an operation due to spina bifida, and he had undescended testicles (cryptorchidism). The baby was two-years-old but could not crawl yet at the time of the final interview.

BIRTH-RELATED OUTCOMES

Only one preterm birth was reported due to preterm labor. This infant was delivered at the 32nd week of gestation (classified as moderate to late preterm birth according to the World Health Organisation) by Caesarean section and had low birth weight (1.5 kg). The infant was hospitalised in the intensive care unit (ICU) due to prematurity related problems. The mother (28-years-old, G3P2) had previously had another preterm birth by Caesarean section and a history of hypertension. The patient was admitted to the ED with Grade 2 severity CO poisoning at 27 weeks of gestation, and completed two HBOT sessions. At the follow-up interview, the baby was three years old. Her parents stated that the baby was healthy with no medical complaints.

The remaining 26 patients delivered term healthy infants with normal birth weights. The median gestational age at birth was 39 (32–42), and the median birth weight was 3,490 g (1,500–4,080 g). The mean birth height was 48.8 cm (SD 3.61). The detailed birth-related outcomes are available in Table 3.

FOLLOW-UP AFTER BIRTH

After birth, the follow-up was continued for 26 of the infants (due to fetal death/medical abortion). The median age of babies was 34 (8–44) months at the last interview. The mean crawling age was found to be 9.2 (SD 2.1) months. The median age at which the infants walked independently was 12 (10–18) months. The median talking age (first words) was found to be 12 (8–24) months. Only one child, who was 43 months old, could not speak as yet. His parents did not report any diagnosed disease.

RELATIONSHIP BETWEEN CLINICAL PARAMETERS, PREGNANCY TRIMESTER AND LONG-TERM FOLLOW-UP OUTCOMES

Transient/prolonged unconsciousness, cardiac abnormality, COHb groups, HBOT delay groups, and pregnancy trimester were compared with long-term infant outcome parameters (birth week, birth weight, birth height, crawling, walking independently and talking [first words] ages). Only one statistically significant relationship was found, between birth weight and pregnancy trimester during CO exposure (P = 0.029). Further binary comparisons for pregnancy trimester were completed. CO poisonings during the third trimester significantly decreased the birth weight. (1st–3rd trimester P = 0.018, 2nd–3rd trimester P = 0.018) though third trimester numbers were small (n = 3) and this is a fragile result (Figure 3).

The linear correlation between clinical severity parameters (COHb, lactate, WBC, pH, delay of HBOT), pregnancy week, and long-term infant outcome parameters (birth week, birth weight, birth height, crawling age, walking independently age and talking [first words] age) were investigated. There was a modest positive correlation between the week of pregnancy during the incident and the age of walking independently (P = 0.043, r = 0.436). (Figure 4)

Discussion

A single episode of hypoxia from CO poisoning can be teratogenic for a fetus.[3] Thus, acute CO poisoning in pregnancy is accepted as an indication for HBOT.[8,9] The largest three studies reported in the literature document good outcomes in terms of long-term follow-up of infants who were subject to HBOT in utero to treat acute CO poisoning.[8,13,16] A number of case reports also detail uneventful long-term infant outcomes following HBOT.[17,18] However in two reports, persistently small head circumference and bladder complications were demonstrated. Both cases had a severe clinical presentation with maternal COHb > 45%.[19,20] In the present study, one pregnancy ended with miscarriage two

Table 3
Birth related outcomes of 27 pregnancies treated with HBOT after CO poisoning; CS – Caesarean section; LBW – low birth weight; VD – vaginal delivery. Note: percentages are calculated on a small sample size

Parameter	*n* (%)
Birth type	
VD	18 (66.6)
CS	8 (29.6)
Abortion	1 (3.7)
Birth week	
Term	25 (96.2)
Moderate to late preterm (32–37 week)	1 (3.8)
Birth weight	
Normal (> 2.5 kg)	22 (95.7)
LBW (1.5–2.5 kg)	1 (4.3)
Not available	3
Sex	
Female	16 (61.5)
Male	10 (38.5)
Intensive care unit necessity	
Yes	1 (3.8)
No	25 (96.2)

weeks after HBOT sessions, one with preterm birth, and one fetal anatomic malformation was recorded. However, these outcomes are possibly incidental, and not related to CO poisoning or HBOT.

In the case of miscarriage, the patient had a previous miscarriage history: a previous pregnancy loss may increase the miscarriage risk for a consecutive pregnancy.[21] In addition, the patient had been experiencing vaginal bleeds both prior to and after the HBOT, and bleeding is one of the most common signs of miscarriage.[22] In a review about air pollution exposure during pregnancy, the relationship between CO exposure and spontaneous abortion in the first trimester was analysed. However, only three studies were available, and the authors felt that the results were inconclusive.[23] Similarly, another study failed to find evidence to relate abortion and HBOT.[8] Taking all of this into account, the bleeding problems in this pregnancy and miscarriage history demonstrates an apparent risk; therefore, the spontaneous abortion is not likely to be related to CO poisoning or HBOT.

In the second adverse outcome, the pregnancy ended with a preterm birth five weeks after the CO incident. Preterm births after CO poisoning are reported in the literature;[7,13,24] nevertheless, preterm birth in CO intoxicated pregnant cases treated with HBOT are rarely reported. One study reported no adverse events after HBOT, although they did note a preterm birth after NBOT.[13] However, another reported premature delivery of a healthy baby at 35 weeks of gestation in a woman who received HBOT due to acute CO intoxication.[8] In the present study, the mother had a previous preterm birth and a history of hypertension; these factors, along with maternal stress are well-known risk factors for premature birth,[25] and thus are more likely to be causative in this case than CO poisoning or HBOT.

In the case of the baby born with anatomical malformation, the mother had CO poisoning at 11 weeks of gestation; at this point, ultrasound examination was normal. However, a lower extremity malformation was diagnosed in the sixth month of the pregnancy; post-partum, the baby was diagnosed with spina bifida and cryptorchidism. Open neural tube defects are common congenital anomalies, with myelomeningocele (spina bifida) being the most common presentation. Neural tube closure in an embryo occurs during the third and fourth weeks after conception. Failure can result in vertebrae, spinal cord, cranial or brain defects.[26] The neurologic deficit depends on the level of the lesion. Meningomyelocele usually leads to complete paralysis and sensation deficits, affecting lower extremities and trunks.[27] These cases often have congenital skeletal deformities and orthopaedic abnormalities. Folate deficiency, genetic factors, syndromes, amniotic bands, maternal hyperthermia, pre-gestational diabetes, obesity, pesticide exposure, nitrosatable drugs, and clomiphene are risk factors for open neural tube defects.[26] Ultrasound examination and maternal serum alpha-fetoprotein are widely used for detection. Transvaginal ultrasound examinations at 12–14 weeks of gestation have low detection rates for spina bifida (44%), while those made in the second trimester have a 92–95% detection rate.[26] In the present case, the ultrasound was reported to be normal in the 11th week of gestation. Maternal alpha-fetoprotein results were not available. The mother (G2P1), who was 19-years-old, lived in a rural area and the CO poisoning occurred from the burning of dried dung for heating. The mother's young age and lower socioeconomic status are the apparent risk factors for NTD.[28] The infant also had cryptorchidism, which is more common in meningomyelocele than the normal population.[29] In conclusion, the complications in this infant are unlikely to be related to CO poisoning or HBOT based on the fact that the CO poisoning and HBOT occurred in the 11th week after physiological neural tube closure in the embryo would have been completed.

The age of crawling, walking independently, and talking (first words) ages were also studied as infant developmental milestones. In two previous studies, psychomotor development and growth were uneventful in infants who received HBOT in utero.[13,16] Similarly, the crawling and walking milestones were in 'normal age range' according to the World Health Organisation and the normative Turkish values.[30,31] The median age for the use of two words other

Figure 3

Box plot of the relationship between pregnancy trimester during CO poisoning and birth weight of infants; the thick line in the box shows the median. The box represents interquantile range. The bars represent the range of data. Data falling outside the lower (Q1) and upper (Q3) quartile range are plotted as outliers of the data.

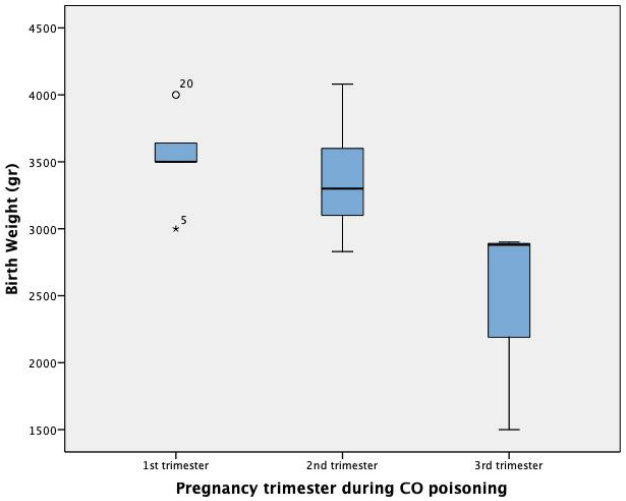
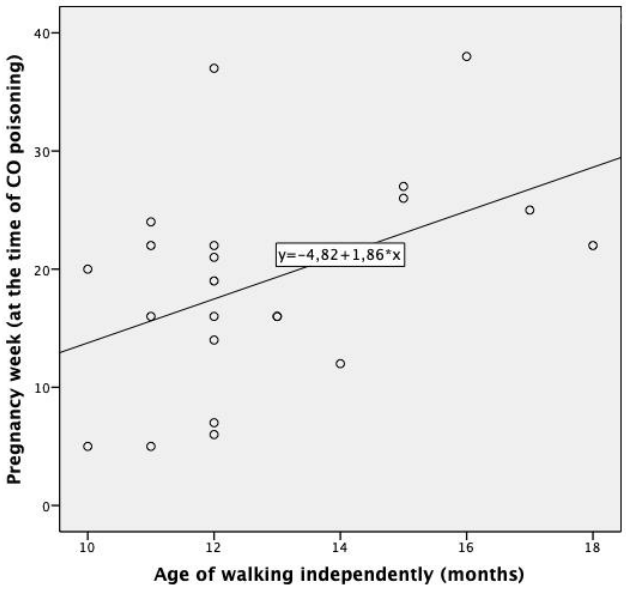


Figure 4

The relationship between pregnancy week during CO poisoning and infants age of walking independently



than mama/dada was reported to be 11 (9.1–14.9) months in a Turkish language development milestones study.[32] Six infants in the present study completed this developmental milestone much later, after 15 months of age. However, these data were gathered retrospectively by telephone interviews with parents in which they might not have remembered correctly or misunderstood the question.

The final aim was to determine the relationship between clinical severity parameters and pregnancy trimester with long-term outcomes of infants who underwent HBOT in utero for acute CO intoxication. Most case reports in the literature are limited with respect to severe CO poisoning pregnant cases.[18–20] Only one compared the severity of the CO exposure and pregnancy trimester at the time of the incident with infants' long-term outcomes. That study found that only severe cases (Grade 4 and 5 severity, $n = 5$) had adverse events in the long-term follow-up. The severe cases without any adverse event during follow-up ($n = 2$) had all received HBOT.[13] None of the present cases following which a live infant was born had Grade 4 or 5 severity; thus, it was not possible to compare these severity groups with long-term outcomes.

Birth weight is a significant indicator of intrauterine growth retardation and is affected by many factors.[33] Low or chronic CO exposure in utero may also affect birth weight.[16] However, the relationship between pregnancy trimester during CO poisoning and birth parameters has received very little attention.[8,16] One study found that the pregnancy trimester in which exposure occurred did not affect mean birth weight.[13] In contrast, CO poisonings during the third trimester were significantly associated with a decrease in birth weight in the present study ($P = 0.018$). To date, trimester effects on birth weight have only been studied with regard to maternal smoking exposure;[34] in a meta-analysis all fetal size, and growth measurements were significantly reduced at the third-trimester. However, maternal smoking did not significantly affect the estimated fetal weight or abdominal circumference in the second trimester.[34] In the present study, only one infant had a low birth weight, only six mothers were active smokers during pregnancy, and every infant had completed at least one HBOT session in utero with 4 (2–13) hours median HBOT delay after CO exposure. However, with such small sample sizes it is impossible to draw a reliable conclusions from these data. The effect of pregnancy trimester on birth weight for CO intoxications should be studied in further clinical trials with greater sample sizes.

The week of pregnancy during poisoning was found to have a modest positive correlation with the age of independent walking ($P = 0.043$, $r = 0.436$), which suggests that the older the fetus at the time of CO poisoning, the more delayed the walking age. Genetic and environmental factors influence walking attainment.[35] However, no other studies have revealed a relationship between CO intoxication and the infant's walking age. On the other hand, delay in walking may be a predictor of a developmental disorder such as cerebral palsy.[35] Cerebral palsy is a known complication of CO poisoning during pregnancy, especially in the last trimester due to hypoxia; however none of the infants in the present study were diagnosed with cerebral palsy.[6] All of the infants in the present cohort could walk before the 18th month, except the infant with lower extremity malformation. Thus, the observation is insufficient to draw a reliable conclusion, and further studies may focus on the mothers' gestational age and infants' developmental outcomes.

The present study covers the largest pregnant patient group receiving HBOT for CO poisoning with the longest follow-up period (8–44 months) in the literature and includes pregnancy, birth, and neurological/motor developmental outcomes. Only one other study is similar in terms of the study population; however follow-up ended at birth.[8] Another similar study did not investigate the effect of HBOT on infants' developmental milestones,[13] while a third compared the effect of HBOT on infants with a normal, non-treated population in terms of only psychomotor development and growth. They did not analyse adverse events during pregnancy and birth.[16]

LIMITATIONS

Important limitations were the absence of an NBOT -treated control group and the absence of Grade 4–5 clinical severity cases. The retrospective nature of the study also lead to the loss of some valuable data; for instance, fetal monitoring tracings of late decelerations, fetal movements, biophysical profile score and head circumference were not recorded. Another concern is that the long-term outcomes were gathered from interviews with parents, who may not have remembered developmental milestones correctly or misunderstood questions. Neurological and motor developmental milestones were limited to crawling, walking independently, and talking (first words). HBOT was mostly completed in only one session in our study. Mothers were unwilling to continue additional HBOT sessions if their symptoms resolved after one session. However, as fetal status cannot be measured effectively, there is no consensus on the optimal total HBOT session number and this could not be analysed in this study.

Conclusions

The adverse events seen in this cohort were likely to be incidental. There was no definite evidence of fetal morbidity or mortality after HBOT for CO poisoning. HBOT may improve short-term and long-term outcomes without any complication in infants poisoned with CO in utero, though definitive conclusions cannot be drawn from a retrospective observational cohort study. Prospective controlled studies with a larger sample size would bring more certainty to conclusions, but may be challenging ethically. Objective data on fetal distress after CO poisoning and HBOT should be gathered prospectively. Similarly, significant developmental indicators such as head circumference at birth should also be included in these studies. Further studies may also focus on describing the best HBOT protocol (total number of sessions) and the optimal time window for the first HBOT session. The relationship between clinical severity parameters and infant outcomes should also be studied to determine the most vulnerable group. In this way, the treatment protocols may be extended for better infant outcomes in high-risk groups.

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