Recording of Complications of Treatment of Hypoxic Ischemic Neonates by Passive Whole-Body Cooling: A Study in Neonatal Intensive Care Unit of Mataria Teaching Hospital

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ABSTRACT

Background: Hypoxic-Ischemic Encephalopathy (HIE) is a type of neonatal encephalopathy where mortality rate is estimated by 11.2%, globally. The only known management for HIE is therapeutic hypothermia. However, many drawbacks have been associated with therapeutic hypothermia including death.

Objective: Recording complications of treatment of hypoxic ischemic neonates using therapeutic hypothermia (TH) for improvement of the results of the management using TH.

Patients and Methods: In this case-series study, which was conducted at the Neonatal Intensive Care Unit (NICU) of Mataria Teaching Hospital (MTH), Cairo, Egypt. The study was conducted from January 2018 to December 2019. All medical files of fourteen neonates presented with HIE and treated with hypothermia were reviewed.

Results: Among the 14 neonates with HIE, survivor cases were 71.6%. They were discharged on single oral anticonvulsant and was weaned off after one month and all were on full oral feeding. One case died on second day of hypothermia due to severe pulmonary hypertension and uncontrolled hypotension (7.1%) and 21.3% had sepsis and 7.1% had early onset and died on 4th day with maternal history of chorioamnionitis and 14.3% died from late onset sepsis.

Conclusion: Although therapeutic hypothermia is a well-established treatment to neonates with hypoxic ischemic disease, their short-term effects can be easily controlled but low incidence of devastating complication can occur. Further controlled studies are needed to detect the factors associated with the elevated risk of such consequences.

Keywords: Hypoxic ischemic neonates, Passive whole-body cooling.

INTRODUCTION

Neonatal Encephalopathy (NE) is a neurological disorder triggered by a disorder of the brain with an incidence of 3 per 1000 live births [(1)]. Symptoms associated with NE include alteration of consciousness, respiratory depression, seizures, and abnormal muscle tone and reflexes [(2)]. Hypoxic-Ischemic Encephalopathy (HIE) is a subtype of NE with characteristic lesions observed in an MRI [(3)]. The rate of HIE is 1.3 to 1.7 per 1000 live full term births [(1)]. The mortality rate associated with HIE is 11.2% (567000 deaths in 2019), globally [(4)] and was previously reported in another study by 15–20% due to complications of perinatal asphyxia [(1)]. Therapeutic Hypothermia (TH) is a useful management for HIE where it must be used within the first 6 h of life [(5)]. This is done through a total body cooling or selective head cooling to 32°C - 34°C in infants ≥ 36 weeks' gestational age [(6)].

In moderate to severe NE, the brain has a phase of secondary injury with nearly whole failure in mitochondrial energy production, cytotoxic oedema, cell death and clinical decline associated with seizures. This usually happens after 6–15 hours of HIE [(7)]. The effect of TH is accomplished through enhancement of apoptosis, reduced loss of high-energy phosphates, decreased oxygen consumption, reduced release of nitric oxide, glutamate, free radicals and excitatory amino acid neurotransmitters, and the initiation of genes that diminish neuronal death [(6)]. Although TH procedure is widely presented in developed countries, which showed a reduction in mortality of risk ratio (RR) 0.78 and improved survival with normal neurological outcome after NE with RR: 1.53. In developing countries, such units are not readily available and care may be sub-optimal. In addition, in low-and middle-income countries the therapeutic time-window for admission to such units in hospitals is delayed as well as the presence of prolonged or obstructed labor, and lack of neonatal transport facilities can cause delayed treatment [(8, 9)].

Therapeutic hypothermia adverse effects:

Although TH is well tolerated in NE, short-term adverse effects can occur such as bradycardia (may occur even on decrease one degree C in temperature), hypotension as a result of decreased cardiac output and respiratory problems such as decreased surfactant production, induced pulmonary vasoconstriction and pulmonary hypertension as well as reduced oxygen delivery. Also, electrolyte imbalance, particularly hypokalemia, hyponatremia, hypomagnesemia, and hypophosphatemia. Additionally, hypothermia can cause platelet dysfunction and increased incidence of sepsis [(9)].

Aim: Recoding all complications associated with treatment of hypoxic ischemic neonates with therapeutic hypothermia (TH) for improvement of the results of the management using TH.

SUBJECTS AND METHODS

This was a case-series study conducted at the Neonatal Intensive Care Unit (NICU) of Mataria Teaching Hospital (MTH) from January 2018 to December 2019.

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All medical files of fourteen neonates presented with HIE and treated with hypothermia were reviewed. Neonates considered hypoxic if pH 7.01-7.15 with base deficit ≥10 mmol/L in the first hour and Apgar score < 5 at 10 minutes and presence of seizures, which denotes moderate to severe encephalopathy [(10)]. Neonates were subjected to hypothermia if they fitted the following criteria: GA ≥ 36 weeks, birth weight ≥ 1.8Kg, and presented within the first 6 hours of his life [(8)]. All complications that were associated with NE treatment with therapeutic hypothermia were recorded as well as the treatment implemented.

Ethical approval:

An approval of the study was obtained from Mataria Teaching Hospital Academic and Ethical Committee. Informed consent was not applicable here since the collected data could not be attributed to specific individual due to unavailability of patient identifier.

Statistics analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

In table (1), mothers of NE babies were mostly between 20-35 years of age and all were Egyptians. All were house wives with secondary level of education. Fifty percent were multiparous. Previous abortions occurred in half of them, one has previous history of HIE baby. All mothers were non-smokers with history of the fathers as smokers (21.4%) and one father had history of drug abuse. More than 42% of the mothers had CS while the rest was assisted vaginally. Regarding maternal diseases, 21% of the mothers had history of illness. For instance, 7.1% had urinary tract infection, 7.1% had pre-eclampsia, and 7.1% were suffering from chorioamnionitis and rupture uterus. All of the fourteen neonates had HIE. Majority of them were males.

Table (1): Demographic data: maternal and neonatal findings:

		Number	Percentage	Rang (Mean± SD)
Maternal Age	< 20 years	3	21.4	18-35 (25.7±6.8)
	20 - 30 years	6	42.9	
	> 30 years	5	35.7	
Gravidity	One	7	50.0	1-6 (2±1.5)
	Two	2	14.4	--
	Three and more	5	35.6	--
Parity	One	8	57.1	--
	Two	2	14.3	--
	Three and more	4	28.6	--
Abortion	No history of abortion	9	64.3	--
	One	3	21.4	--
	More than once	2	14.2	--
Similar conditions to hypoxia	No similar condition	13	92.9	--
	Similar condition	1	7.1	--
Maternal Illness	No Maternal illness	11	78.6	--
	Maternal illness	3	21.4	--
Mode of delivery	Vaginal	8	57.1	--
	CS	6	42.9	--
Work of Mother	Not working	14	100.0	--
	Working	0	0.0	--
Smoking	Non-Smoker	11	78.6	--
	Smoker	3	21.4	--
Drug Abuse	No Drug Abuse	13	92.9	--
	Drug Abuse	1	7.1	--
Rupture uterus	No rupture uterus	12	85.7	--
	Rupture uterus	2	14.3	--

CS: cesarean section

The gestational age ranged from 36-42 weeks with a mean of 38 weeks. All were admitted in their first day of life. Half of them had birth weight of 2.5 kg with mean weight of 3 kg. 25% of cases were classified as 3rd grad HIE and 75% of cases were classified as 2nd grade HIE according to Sarnat & Sarnat classification **(10).**

Fractional inspired oxygen (FiO2) more than 30% was administered in 83.4% of infants. Bolus saline administered during resuscitation in 35.7% of cases (more than once in 21.4%) while sodium bicarbonate was given in 28.6% of cases (Table 2).

All neonates had severe metabolic acidosis [pH ranged from 6.8-7.04 (mean 6.9±0.9)], bicarbonate deficit ranged from -10.6 mmol/L to -18.7 mmol/L with a mean of 14.81±2.39 (Table 3).

All met the criteria for starting cooling to hypoxic ischemic neonates (8-10)**.** All neonates were intubated to give deep sedation and TH protocol was started within 6 hours of birth as all cases were delivered in Mataria hospital. At the first, Servo heater was turned off until criteria for cooling were evaluated and recorded. Period of TH was done for 72 hours followed by rewarming for 6-12 hours. Targeted temperature gained within an hour in 64.3% of cases, after 2 hours 21.4% gained the targeted temperature, and in more than 2 hours in 14.2%. TH was stopped in one case on the second day. While rewarming was started after 72 hours in 93% of the cases. No one had intracranial hemorrhage before starting TH protocol.

Also, heart rate ranged from 40-190 bpm, seven percent of cases suffered tachycardia which was controlled by increasing sedation and 7.1% suffered severe bradycardia. Systolic blood pressure ranged from 50-86 mmHg and diastolic blood pressure ranged from 24-57 mmHg and pulmonary hypertension was detected in 21.4% of cases.

Cooling was stopped on third day in one case because of severe pulmonary hypertension and uncontrolled hypotension (Table 2). No one had Skin fat necrosis, edema, or petechial rash. All had seizures. Seizures developed within 3 hours and was managed by single anticonvulsant in 28.6% of cases, 14.2% needed double anticonvulsants and the rest needed triple anticonvulsants. No Seizure was re-emerged after rewarming.

Table (2): Infants clinical data (resuscitation, assessment for therapeutic hypothermia, clinical data, feeding, hospital stay and outcome)

		Number	Percentage	Range (Mean± SD)
	Basic data			
Gestational age (weeks)	36	2	14.3%	36-42 (38.1±1.6)
	37	3	21.4%	--
	38	5	35.7%	--
	39	1	7.1%	--
	40	2	14.3%	--
	42	1	7.1%	--
Weight	< 2.5 kg	1	7.1%	2.5-4 3±0.43
	2.5 - kg	7	50.0%	--
	3 - kg	4	28.6%	--
	3.5 - kg	2	14.3%	--
Sex	Female	4	28.6%	--
	Male	10	71.4%	--
Apgar-1	0	7	50.0%	0-1 (0.5±0.5)
	1	7	50.0%	
Apgar-5	0	3	21.4%	0-4 (1.8±1.2)
	1	2	14.3%	--
	2	4	28.6%	--
	3	4	28.6%	--
	4	1	7.1%	--
Apgar-10	2	1	7.1%	2-5 (3.9±0.9)
	3	4	28.6%	--
	4	4	28.6%	--
	5	5	35.7%	--
Resuscitation				**Range (Mean±SD)**
Resuscitation	Resuscitated	14	100.0%	--
Intubation	Absent	3	21.4%	--
	Present	11	78.6%	--
Oxygen	oxygenated	14	100.0%	--
Adrenaline	Absent	8	57.1%	--
	Present	6	42.9%	--
Saline	Absent	9	64.3%	--
	Present	5	35.7%	--
Na HCO3 injection	Absent	10	71.4%	--
	Present	4	28.6%	--
Peripheral access	Absent	1	7.1%	--
	Present	13	92.9%	--
UVC	Absent	7	50.0%	--
	Present	7	50.0%	--
	89.00	1	7.1%	--
	90.00	1	7.1%	--
	100.00	2	14.3%	--
	120.00	1	7.1%	--
	129.00	1	7.1%	--

		Number	Percentage	Range (Mean± SD)
	130.00	1	7.1%	--
	142.00	1	7.1%	--
	231.00	1	7.1%	--
Clinical assessment				
Tachycardia	Absent	13	92.9%	--
	Present	1	7.1%	--
Bradycardia	No	12	85.7	--
	Yes	2	14.3	--
Off cooling	Complete	13	92.9%	--
	Incomplete	1	7.1%	--
Bleeding	Absent	14	100%	--
	Present	0	0%	--
Skin (subcutaneous fat necrosis)	Absent	14	100%	--
	Present	0	0%	--
Pulmonary hypertension	Absent	11	78.7%	--
	Present	3	21.3%	--
Sepsis	No	7	(50%)	--
	Yes: Early onset sepsis Late onset sepsis	7 5 2	 (35.8%) (14.2%)	--
Hospital progress				**Range (Mean± SD)**
Oral feeding	0	2	7.1%	0-10 (5.7± 4.6)
	4	4	7.1%	--
	5	2	7.1%	--
	6	3	7.1%	--
	7	1	14.3%	--
	10	2	14.3%	--
Ventilation period (days)	2	1	7.1%	2-22 (6.3±5)
	3	2	14.3%	--
	4	2	14.3%	--
	5	2	14.3%	--
	6	3	21.4%	--
	7	1	7.1%	--
	9	1	7.1%	--
	22	1	7.1%	--
	80	1	7.1%	--
Hospital Days	2	1	7.1%	2-30 (15.6 ± 8.1)
	3	1	7.1%	--
	9	1	7.1%	--
	12	1	7.1%	--
	13	1	7.1%	--
	14	1	7.1%	--
	16	1	7.1%	--
	18	1	7.1%	--
	20	2	14.3%	--
	22	1	7.1%	--
	25	1	7.1%	--
	30	1	7.1%	--
Outcome	Died	4	28.6%	--
	Survived	10	71.4%	--

Table (3): First ABG:

	Range	Mean ±SD
pH	6.8-7.04	6.93±0.09
CO2	14.0- 45.0	30.21±7.32
HCO3	5.0- 12.0	9.19±2.11
Deficit HCO3	(-10.6)- (-18.7)	-14.8± 2.39

The hematological evaluation showed that prothrombin time increased in 21.4% of cases with no manifest bleeding as plasma transfusion and vitamin K were given regularly. Hypokalemia was reported in 2 cases on the second day of cooling and was controlled by adding potassium chloride for 2 days without rebound hyperkalemia. No disturbance was detected in sodium or calcium levels. Hyperglycemia was present in 14.2% of cases and was controlled by decreasing glucose concentration only (Table 4).

Table (4): Laboratory finding

	Mean	SD
Platelet (mcL)	202.79	49.16
WBCs (cells/μL)	16.66	3.90
INR	1.25	0.36
Na (mEq/L)	137.38	31.56
K (mEq/L)	4.68	0.81
Ca (mg/dL)	0.99	0.27
RBG (mg/dL)	97.42	21.31

In table (5), 36% of the cases were presented with a serum C-reactive protein (CRP) of > 24. Nevertheless, 54.4% of the cases had negative serum CRP. Acute kidney disease was found in only one case where urea concentration was 106 mg\L and serum creatinine were 0.9 mg/dl. Normal liver function was detected in all the cases. In culture results, blood culture was positive in 5 cases while 2 had sputum positive culture.

Table (5): Inflammation detection and kidney injuries

Result	N (%)	Result	N (%)	Results	N (%)
CRP:	6 54.5%	**AKI:**		**Culture**	
Negative:				• Positive Blood culture Positive	5 (35.5%)
• 12-24	1 (9.1%)	• No	13 (92.9)		
• >24	5 (36.4%)	• Yes	1 (7.1)	• Sputum culture	2 (14.3%)

CRP: C- reactive protein; AKI: Acute kidney injury

Feeding and discharge:

Feeding has started between 4-10 day of life, maximum feeding amount reached on day 9-20 days of life, full suckling (oral feeding) was observed within 10-20 days while 2 cases have stopped enteral feeding due to sepsis on Day 7 and 8 and 2 cases did not start feeding because they died on 2nd and 4th day as shown in table (3).

Among the 14 neonates with HIE, survivor cases were 71.6%%. They were discharged on single oral anticonvulsant and was weaned off after one month and all were on full oral feeding. One case died on second day of hypothermia due to severe pulmonary hypertension and uncontrolled hypotension (7.1%), 21.3% had sepsis, 7.1% had early onset and had maternal history of chorioamnionitis and 14.3% died from late onset sepsis. All cases were on low setting ventilator from first day of admission. Non-survived cases could not wean from ventilator till death. Ventilator days ranged from 2-80 days in non-survivor and in survivor group they ranged from 4-7 days. Hospitalization days ranged from 3-30 days in survivor groups and 2—22 days among non-survivors as shown in table (2).

Cranial sonar was done to all neonates to exclude intracranial hemorrhage. Echocardiography was done to exclude cardiomyopathy and estimate pulmonary hypertension.

DISCUSSION

Neonatal encephalopathy is the most serious illness that can have negative consequences including death, cerebral palsy, epilepsy and cognitive disability [(11)]. Associated risk factors have been studied extensively to predict the most abundant causes and manage it as early as possible [(12)]. In one study, mothers had previous cesarean delivery were associated with increased risk of HIE (OR 3.66; 95% CI: 2.41– 5.55) [(11)]. Another has revealed that among the maternal risk factors that could lead to increased risk of HIE were substance-related diagnosis, preeclampsia, and infection, which increased the incidence to two-fold. The study also found that babies born at 35 or more weeks of gestation had 2.3 per 1000 births incidence of HIE. Also, obesity,

nulliparity, older maternal age, depression, diabetes or hypertension, as well as short or long gestations can predict HIE [13]. This comes in line with our study results where gestational age (ranged from 36-42), maternal illnesses (21.3%), abortion of more than once, and parity in 57.1% were all predominant to NE. As well, males were predominates compared to females in one study [4], which comes in the same line with our study results. In the contrary, a study has reviewed 4165 neonates to reveal that asphyxia indicators like birth events, intrauterine experience to inflammation, fetal growth restriction, and birth defects were associated with NE. However, half of the NE neonates could not be linked to specific risk factors [14, 15].

Regarding Apgar score characteristics in HIE neonates, our sample revealed that about 57% of neonates showed Apgar 2 and 3 at 5 minutes while 92% of them had Apgar 3, 4, and 5 at 10 minutes revealing high incidence of bad consequences. These results come in the same line with **Laptook *et al***. [16] study where Apgar scores at 10 minutes was considered predicted tool in HIE neonates. The study has revealed that death or disabilities were proportional to low 10-minute Apgar scores. Although Apgar scores of < 3 is common to be associated with death and morbid disabilities but it cannot depend on this value to stop resuscitation [16].

Therapeutic hypothermia in our sample was conducted for 72 hours followed by rewarming for 6-12 hours. Targeted temperature gained within an hour in 64.3% of cases, after 2 hours in 21.4% gained the targeted temperature, and in more than 2 hours in 14.2%. TH was stopped in one case on the second day. While rewarming was started after 72 hours in 93% of the cases. This is similar to what have been reported in other studies regarding the timing of TH in neonates to achieve the best therapeutic outcomes with the least side effects. In one study, TH of the brain was approximately 32°C to 34°C starting within the first 5.5 hours after HIE and continued to cool for 12 to 72 hours followed by slow rewarming (0.5°C/hour) [5,6]**.** Another metanalysis has summarized the results of 6 clinical trials regarding the timing and predicted outcomes of TH to reveal a reduction in death or other neurological disability to 25% of neonates in which 32% of infants had moderate NE and 18% had severe encephalopathy [18]. Additionally, rewarming after 72 h of TH was recommended by another study with a complete rewarming within 4–12 h and follow-up using vital signs, respiratory, and circulatory conditions are required [19].

Clinical assessment of neonates in this study revealed hypotension arrhythmia in 14.2%, while in the study of **Tsuda *et al.*[20],** arrhythmia was present in 1.4% and hypotension was revealed in 34.8% of neonates subjected to hypothermia and this can be attributed to early use of inotropes in our study. While pulmonary hypertension was detected in 21.4% of cases in our study which runs with the study of **Eicher *et al.*** [21] who found that 29% of cooled neonates require treatment with inhaled nitric oxide for pulmonary hypertension. Subcutaneous fat necrosis was not reported in our study in contrast to **Tsuda *et al.*** [20] study who found subcutaneous fat necrosis in 0.45 of cases. This may be attributed to the larger sample size in their study. In **Tsuda *et al.*** [20] study, death was detected in neonates with elevated heart rates. These clinical features are subjected to improvement following TH in many studies [18, 22-23].

Hematological assessment of neonatal blood was also recorded in this study where prothrombin time was increased in 21.4% of cases with no thrombocytopenia or manifest bleeding. This is similar to **Eicher *et al.*** [21], who revealed that manifest bleeding was rare in spite of abnormal coagulation profile. In contrast to **Tsuda *et al.*** [20] study where 13.2% suffered from high coagulation profile bleeding and /or thrombocytopenia as hypothermia inhibit enzymatic reactions of coagulation cascade [24]. Intracellular shift of potassium secondary to hypothermia due to stimulation of beta adrenergic and Na-K ATPase [25], which needed wise correction of hypokalemia to avoid hyperkalemia on rewarming [26].

In our study hypokalemia was reported on the second day of cooling in 14.2% of cases, which is lower than that found in the study of **Eicher *et al.*** [21] (23%) in which there was no difference between hypothermic and normothermic groups in their study. Also **Buse *et al.*** [27]**,** systematic review found that 39 studies of 50 revealed low potassium on the start of hypothermia. Acute kidney disease was found in only one case (7.1%), which is comparable with **Eicher *et al.*** [21] study who found that renal failure was present in 6% in neonates treated with hypothermia. Hyperglycemia was present in 14.2%% of cases. Although there was no statistical difference of glycemic profile of neonates under treatment by hypothermia but neonates with hyperglycemia had less injury [28] to other organ due to the effect of stress hormone, entire gluconeogenesis and reduction of glucose consumption [29].

In addition, 36% of the cases were presented with a serum C-reactive protein (CRP) of > 24, and blood culture was positive in 5 cases while 2 had sputum positive culture. In comparison with other studies, lymphocyte counts peaked in the first 2 hours of age in all insult types after 4 to 6 hours. They reached normal levels. Red blood cell counts peaked between 6 and 8 hours of age and returned to normal after 36 to 72 hours of age with no association found between hematologic counts and adverse outcome in NE [30]. Another study has revealed a CRP value in only 15.8% of the patients. Also, 76.9% of the patients had higher LDH values which was recommended as a good predictor of HIE in the first 12/24 h after birth [31]. TH acts through its effect on C-reactive protein

(CRP) where it delays their rise and response to eventually decreased white cell count and neutrophil count [32]. The effect of hypothermia on decreasing the release of inflammatory biomarkers should be closely monitored and considered while entering antibiotics as well as the duration for neonates with NE. Consequently, a complete sepsis assessment is vital in those babies [2]. Moreover, occurrence of perinatal sepsis is higher in low and middle-income countries than in high-income countries [33].

In our study, early onset sepsis was less than late onset sepsis almost by the half. In **Tsuda *et al.*** [17] study, early sepsis was 0.8%, while **Jacob *et al.*** [5], did not detect sepsis following hypothermia which could be attributed to the use of antibiotics in his study.

Oral feeding in NE in our sample was started on day 10 of life, which was preceded by oro-gastric feeding from day 4. Feeding stopped in 14.2% of cases due to NEC. 71.6% of cases took their full feeding by suckling before discharge. However, oropharyngeal dysphagia (OPD) has been reported in the majority of HIE neonates with incomplete arousal during breastfeeding and fewer obvious rooting, lower latching onto the breast, and more single sucks in comparison with normal newborns [34]. Another study has revealed that 31% of HIE neonates were fed during treatment. Where 0.1% had severe necrotizing enterocolitis. Interestingly, the enterally fed neonates in this study showed fewer late-onset infections with higher survival to discharge and higher percentage of breastfeeding at discharge with shorter hospital stays compared to the unfed group [35]. While according to **Tsuda *et al.*** [17] study, 75% of cases were on suckling, and full oral feeding was established in 81.4% of cases during initial hospital admission [17].

Hypothermia was reported to have a negative impact on pulmonary functions. It can increase pulmonary vascular resistance, decrease oxygen release, and reduce oxygen consumption. In our study, weaning from Mechanical ventilation (MV) was between day 4-24 in 92.9% and 7.1% needed persistent MV. While in **Tsuda *et al.*** [17], 86.3% weaned after 11.2± 27.0 days, whereas 9.7% required persistent mechanical ventilation.

Death rate was reported by one study to be 2.7% in before discharge, which was lowered following strict adherent application in initiation of TH and decrease in the severity of NE [17]. However, death rates reported by others are similar to our study report (28.5%) [22, 23]. Discharge days were also similar to that reported by **Tsuda and colleagues** [17].

CONCLUSION

Although therapeutic hypothermia is a well-established treatment to neonates with hypoxic ischemic disease, their short-term effects can be easily controlled but low incidence of devastating complication can occur. Further controlled studies are needed to detect the factors associated with the elevated risk of such consequences.

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