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Research Article

Evaluation of Fetal and Neonatal Thyroid in Pregnancies with Covid-19 Infections

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Abstract

Objective: To study the effect of coronavirus disease (COVID-19) on the thyroid gland of the newborn babies of pregnant mothers with COVID-19.

Design: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the most lethal disease encountered recently, otherwise known as Coronavirus disease (COVID-19). COVID-19 causes pulmonary and systemic inflammation which produces multiorgan dysfunction. The thyroid gland is one of the important organs targeted by the disease. Pregnant mothers infected with SARS- CoV-2 have been shown to transmit the virus to their fetuses and newborns.

Patients: Newborn babies of COVID-19 infected mothers are admitted to a negative pressure isolation room in neonatal intensive care unit (NICU) and managed according to their clinical conditions. A polymerase chain reaction (PCR) test for COVID-19 is carried on all babies at the age of 24 hours.

Measurements: Thyroid-stimulating hormone (TSH) estimation was measured in these babies at the age of one to 24 hours and repeated at the age of 72 hours together with free thyroxine (FT4).

Results: Ninety-five babies were delivered to pregnant mothers with COVID-19. Three babies had positive PCR while the rest were negative. TSH values were abnormally high in 48% of the babies while FT4 values were abnormally high in 69% of these babies.

Conclusion: COVID-19 in pregnant mothers tends to exert its effect on the thyroid gland of the newborn by direct injury as the virus is known to be transmitted from the mother to her fetus. Thyroid functions of the newborns born to COVID-19 infected mothers were abnormal.

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Keywords: *Neonatal Thyroid; Covid-19; SARS-CoV-2*

Abbreviations

COVID-19: Coronavirus Disease; TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxine; mIU: Milli-International Unit; pmol: Picomol

Introduction

Screening for hypothyroidism is offered to all newborn babies in Saudi Arabia. In Security Forces Hospital we continue to monitor TSH in the newborn babies at the age of 1 - 24 hours in addition to the national metabolic screening program. FT4 is measured when the

TSH values are abnormal. During TSH screening it was noticed that babies born to mothers with COVID-19 infection had significantly abnormal TSH values. There are no current data on the effect of COVID-19 pregnancies on the newborn thyroid gland. All the literature related to involvement of the thyroid in COVID-19 comes from adult studies. Adult studies report that those adults who were infected with COVID-19 had their thyroid glands afflicted through possible direct insult, immune mechanisms or inflammatory immune response (cytokine storm). The common thyroid disorders seen after COVID-19 in adults included hyperthyroidism, subacute thyroiditis (SAT) and hypothyroidism.

Objective of the Study

To evaluate the thyroid function tests in babies born to pregnant mothers with COVID-19 infection. To define the presence of thyroid disease in those babies who have abnormal thyroid function tests whether temporary or permanent.

Methods

This is an observational study which monitors TSH and FT4 values in all newborns born during the COVID-19 pandemic in the period from May 2020 to September 2021. TSH is used as a screening test for hypothyroidism in all newborns in Saudi Arabia. For our study blood sample for TSH is obtained at the age of 1 - 24 hours. Normal range for TSH in our laboratory is 0.3 - 7.2 mIU/l. Babies with TSH values 35 mIU/l or above are evaluated further for hypothyroidism by estimation of FT4 (Normal range 12 - 22 pmol/l). TSH estimation is repeated at 72 hours of age together with FT4. Thereafter both TSH and FT4 are requested as needed.

Values of FT4 above 30 pmol/l are followed to confirm or rule out hyperthyroidism.

Results of thyroid functions in babies of COVID-19 pregnancies were compared to other newborns delivered after normal pregnancies in the same period of the study.

Data of associated medical disorders occurring with these pregnancies were recorded including hypothyroidism, hyperthyroidism and diabetes mellitus.

Babies with severe congenital malformations were excluded.

The study was approved by the hospital research and ethical committees.

Informed consent was obtained from the guardians of the babies.

Statistical analysis

Descriptive analysis was performed to present the results. Categorical variables were described as numbers and percentages. Continuous variables were presented as mean ± standard deviation or range (minimum-maximum value). A sub-group analysis was used for patients with elevated TSH levels at birth and elevated FT4. Changes in TSH and FT4 levels at birth and 72 hours were compared using paired T-test. Line graphs were used to illustrate the changes of the TSH and FT4 values. Statistical analysis was performed using SPSS 21.0 software (IBM Corp, Armonk, NY).

Results

Study population

The total number of babies born during the period of the study was 6745 babies. Mean birth weight was 2900 grams.

Ninety-five neonates were born to mothers with COVID-19 infection. Mean birth weight was 2883 grams (range 825 - 3870 grams). Forty-seven babies (49.5%) were males and 48 (50.5%) were females.

Ninety-two babies had a negative PCR result for COVID-19 while three babies had positive PCR result. None of the babies was symptomatic and all had an uneventful clinical course.

Thyroid function tests

Results of the thyroid function tests are summarized in table 1. Forty-six babies (48.4%) were found to have elevated TSH values above 35 mIU/l at the age of 1 - 24 hours. Sub-group analysis was conducted for these 46 babies with elevated TSH values. Forty-four babies were included in the sub-group analysis because 2 babies had missing 48 - 72 TSH results. Mean TSH at 1 - 24 hours was 57.1 mIU/l. In all of the 44 babies the elevated TSH values dropped to within normal range after 48 - 72 hours (Figure 1). Compared to TSH values within the first 24 hours there was 78% drop in TSH values at 48 - 72 hours to normal levels (57.1 mIU/l versus 12.4 mIU/l, $p < 0.001$).

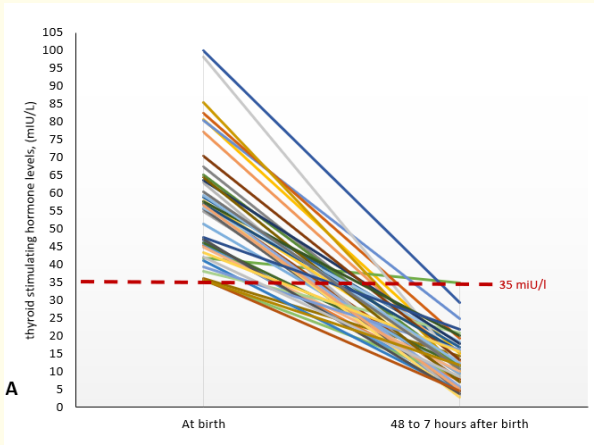

Figure 1A: *Line graph: Changes in individual TSH values in newborns with high TSH.*

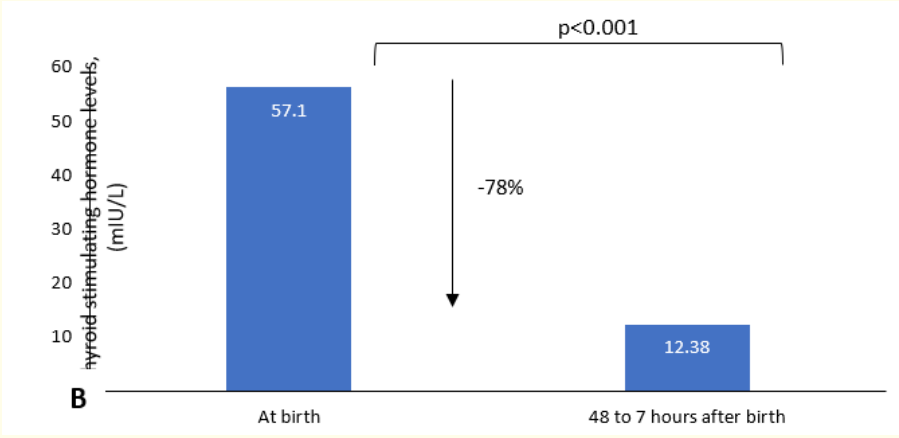

Figure 1B: *Bar graph: Change of mean TSH values (n = 46).*

Variable	Mean	Minimum	Maximum
TSH at birth, mIU/l	36.9	3.59	100
TSH at 48 to 72 hours, mIU/l	11.0	1.55	35
FT4 at birth (n = 46), pmol/L	20.7	12.2	33.1
FT4 at 72hours (n = 46), pmol/L	27.5	14.6	43.3

Table 1: *Thyroid functions of newborns of COVID-19 pregnancies.*
TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxine.

Free thyroxine (FT4) values of the babies with elevated TSH within first 24 hours were within normal range and were observed to be above normal in 69% of babies after 72 hours. There was significant increase in mean FT4 value at 12 hours after birth as compared to FT4 values at birth (19.9 pmol/l versus 27.65 pmol/l. p = < 0.001). Table 2 demonstrates the individual changes of FT4 in the first 24 hours and after 72 hours of birth in 33 babies with FT4 values.

	At Birth (Pmol/L)	72 Hours After Birth (Pmol/L)	% Change	Change	Note
Pt 5	21.18	34.65	64%	Increased	Above normal
Pt 15	18.6	32.8	76%	Increased	Above normal
Pt 16	16.6	30.6	84%	Increased	Above normal
Pt 19	15.7	22	40%	Increased	Normal limits
Pt 25	32.7	19.1	-42%	dropped	Normal limits
Pt 27	16.68	33.4	100%	Increased	Above normal
Pt 29	20.97	31.7	51%	Increased	Above normal
Pt 30	20	20.6	3%	Increased	Normal limits
Pt 31	12.3	25.1	104%	Increased	Slightly above normal
Pt 33	15.1	18.7	24%	Increased	Normal limits
Pt 34	23.1	27.5	19%	Increased	Slightly above normal
Pt 37	20	36.6	83%	Increased	Above normal
Pt 38	17.1	43.3	153%	Increased	Above normal
Pt 39	21.4	26	21%	Increased	Slightly above normal
Pt 41	28.1	27.8	-1%	unchanged	Slightly above normal
Pt 45	27	27.1	0%	unchanged	Slightly above normal
Pt 49	24.9	33.8	36%	Increased	Above normal
Pt 51	15.9	34.8	119%	Increased	Above normal
Pt 58	12.2	22.6	85%	Increased	Slightly above normal
Pt 59	16.3	29.8	83%	Increased	Above normal
Pt 62	14.5	20.9	44%	Increased	Normal limits
Pt 65	28.7	17.2	-40%	dropped	Normal limits
Pt 66	14.7	25.8	76%	Increased	Slightly above normal
Pt 69	15.2	28.3	86%	Increased	Above normal

Pt 73	19.82	19	-4%	dropped	Normal limits
Pt 74	20.72	35.8	73%	Increased	Above normal
Pt 77	22.5	22.1	-2%	dropped	Normal limits
Pt 78	26.1	27.8	7%	Increased	Slightly above normal
Pt 80	18.2	26.4	45%	Increased	Slightly above normal
Pt 81	17.3	27.2	57%	Increased	Slightly above normal
Pt 86	23.7	31.9	35%	Increased	Above normal
Pt 92	22	25.4	15%	Increased	Slightly above normal
Pt 95	17.8	26.7	50%	Increased	Slightly above normal

Table 2: *Changes in FT4 values of newborns with High TSH values at birth (n = 33).*
**Normal values used 12 to 22 picomoles/L.*

Further analysis showed that among the 46 babies with elevated TSH values at 1-24 hours of age, 33 babies had FT4 values recorded in the first 24 hours and after 72 hours of birth. All the babies had normal FT4 values in the first 24 hours (none had FT4 value below 12 pmol/l). After 72 hours the FT4 values were increased in 27 babies, unchanged in 2 babies and dropped in 4 babies to within normal values (Figure 2).

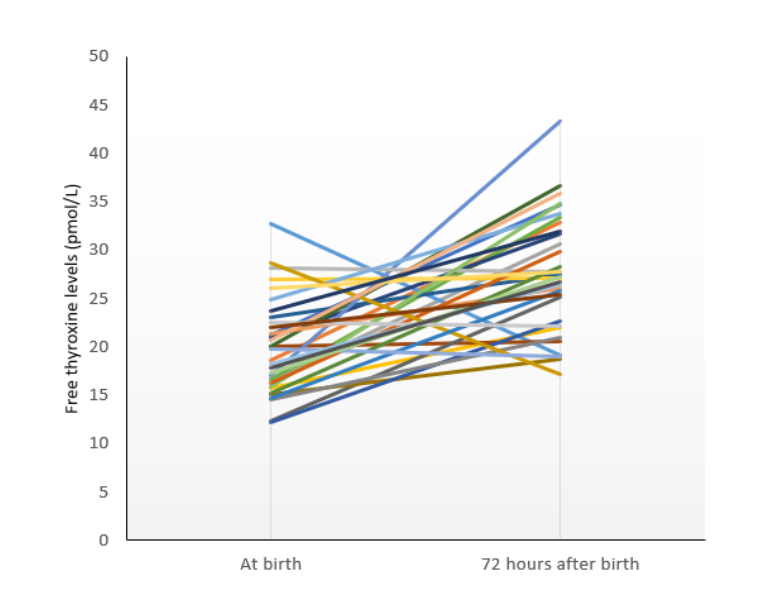

Figure 2: *Line graph: Changes in FT4 values in newborns with high TSH (n = 33).*

TSH values in 6650 babies who were born to mothers without COVID-19 infection during the period of the study showed a mean of 6.2 mIU/l (range 5.0 - 9.23).

Thus, TSH at birth was significantly higher in babies born to mothers with COVID19 infection when compared to TSH of babies of mothers without COVID19 infection (36.9 mIU/l versus 6.2 mIU/l), $p < 0.001$.

Maternal data

Table 3 summarizes the maternal data of the study sample. The majority of the mothers (61.9%) were diagnosed with COVID-19 infection one to two days before delivery. Twenty-eight (34.4%) of the mothers had pre-existing hypothyroidism. Among these 28 mothers, 12 (42.9%) had babies with elevated TSH within the first 24 hours. Furthermore these 12 babies had increased FT4 levels but their TSH normalized at 47 - 72 hours (Table 4).

Variable	Value
Days of COVID-19 diagnosis before delivery	2.8 ± 2.5
Number diagnosed with COVID-19	95
At 1 day	45 (48.9)
2 days	12 (13.0)
3 days	11 (12.0)
≥4 days	27 (29.3)
Pre-existing Medical Condition	
Hypothyroidism	28 (30.4)
Cholestasis	2 (2.1)
Diabetes mellitus	1 (1.1)
Insulin depended diabetes mellitus	3 (3.2)
G6PD	1 (1.1)
GDM	18 (18.9)
Hepatitis B	1 (1.1)
PET	2 (2.1)

Table 3: *Maternal data.*

G6PD: Glucose-6-Phosphate Dehydrogenase; GDM: Gestational Diabetes Mellitus; PET: Pre-Eclamptic Toxemia.

Patient	TSH at Birth (mIU/l)	TSH 48 - 72 hours (mIU/l)	Percentage change in TSH values (%)	FT4 at birth (pmol/L)	FT4 at 72 hours (pmol/L)	Percentage Changes in FT4 values (%)
Pt 15	80.66	15.24	-81.1%	18.6	32.8	76.3%
Pt 19	41.95	35	-16.6%	15.7	22	40.1%
Pt 31	46.13	11.64	-74.8%	12.3	25.1	104.1%
Pt 37	57.95	11.6	-80.0%	20	36.6	83.0%
Pt 45	85.48	10.22	-88.0%	27	27.1	0.4%
Pt 48	41.18	4.62	-88.8%	Missing	24.1	
Pt 49	65.09	11.72	-82.0%	24.9	33.8	35.7%
Pt 59	98.29	11.9	-87.9%	16.3	29.8	82.8%
Pt 68	63.57	17.8	-72.0%	29.3	Missing	
Pt 92	47.72	21.82	-54.3%	22	25.4	15.5%
Pt 93	35.94	4.7	-86.9%	Missing	32.7	
Pt 95	35.76	11.8	-67.0%	17.8	26.7	50%

Table 4: *Thyroid functions of newborns of mothers with COVID-19 and hypothyroidism.*

Pt: Patient; TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxine.

Discussion

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most lethal infection encountered recently and referred to as coronavirus disease (COVID-19). The spike proteins covering the coronavirus bind to angiotensin-converting enzyme 2 (ACE2) receptors which are present on the epithelial surface of human cells. SARS-CoV-2 recruits a serine protease known as transmembrane protease serine 2 (TMPRSS2) which facilitates priming and entry of the virus to the cytoplasm [1]. Thus ACE2 and TMPRSS2 are both involved in entry into the host cells playing an important role in the pathogenesis of COVID-19. SARS-CoV-2 receptors (ACE2) are expressed on broad range of human organs with the highest levels of expression and activity found in the small intestine, kidneys, heart, salivary glands, testicles and thyroid gland [2]. The widespread expression of ACE2 receptors may explain the variety of symptoms and spectrum of organ failure occurring in patients with COVID-19. The presence in abundance of ACE2 receptors in the thyroid parenchyma makes the gland susceptible to SARS-CoV2 injury once the infection has occurred [3].

As there are no data on neonatal thyroid exposure to COVID-19, the literature on the etiology and pathogenesis of thyroid dysfunction after COVID-19 come from adult studies and postmortem findings in those inflicted by the infection. Different mechanisms have been suggested to explain the involvement of the thyroid in SARS-CoV-2 infection.

The first possible mechanism of involvement is the direct influence of SARS-CoV-2 on the thyroid gland. This can be explained by the fact that the thyroid gland is firmly attached to the wall of the trachea which would facilitate the invasion of the gland by the virus directly through the upper respiratory tract. Recent evidence shows that SARS-CoV-2 is present in the serum from COVID-19 patients indicating episodes of viremia which in presence of highly expressed ACE2 in the thyroid follicular cells will damage the gland [4]. Extrapolation of the direct damage of the thyroid gland can be made from previous postmortem studies of SARS-Cov-1 which revealed follicular cell destruction, extensive apoptosis and fibrosis in the absence of lymphocytic infiltration representing the histopathological features of destructive thyroiditis [5].

The second possible mechanism of involvement of the thyroid is by indirect injury through abnormal immune-inflammatory responses to the virus involving coagulation, cytokines and complement systems. This is characterized by strong release of proinflammatory cytokines and results in hyperinflammatory states leading to multiorgan failure and death (cytokine release syndrome or cytokine storm) [6].

Nonthyroidal illness syndrome (NTIS) has been suggested as a third possible mechanism for thyroid disease in COVID-19 infection. Severe or prolonged COVID-19 course produces low serum TSH, T3 and FT4 due to the effect of systemic inflammation caused by the viraemia [3].

SARS-CoV2 produces low thyroid functions due to a primary thyroid injury or a secondary injury at hypothalamic or pituitary level. Dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis was suggested by Leow., *et al*. as they reported 3 cases of central hypothyroidism in their series. These cases recovered spontaneously within 3 - 9 months [7].

Studies on COVID-19 pregnancies have confirmed the transmission of the virus from mothers to their fetuses [8,9]. Our study shows that the babies who were born to mothers with COVID-19 were possibly exposed to the virus for 2 - 5 days in-utero with 71.5% of the exposure occurring in the first three days after confirmation of the infection. However, the PCR was positive in only three babies.

The TSH results in all babies born to COVID19 mothers were significantly higher than TSH results in babies born in the same period to mothers without COVID 19 infection (meanTSH 36.9 mIU/l versus 6.2 mIU/l).

The thyroid function tests results in our study revealed abnormally high TSH values in 48.4% of the babies of COVID-19 pregnancies at the age of 1 - 24 hours (mean TSH 57.1 mIU/l) which dropped to normal values within 48 - 72 hours. On the other hand, FT4 values in

the babies with high TSH were normal at 1 - 24 hours but increased to significantly abnormally high values after 72 hours in 69% of these babies. In fact, the FT4 values at 12 hours after birth showed significant increase compared to FT4 level at 1 hour {19.9 pool/l versus 27.65 pool/l, p = < 0.001}.

It is well known that TSH values in the newborn tend to have a surge in the first four days after birth reaching up to 26.5 mIU/l but fall after that to the normal values. However, the high TSH values in the babies of COVID19 were significantly higher that they cannot be simply explained by the normal surge seen in normal newborns in the first four days of life. In Clinical set up where half of the babies of the COVID19 pregnancies had a mean TSH of 57.1 mIU/l and reaching up to 100 mIU/l, one cannot interpret these results as a normal surge of TSH and hence the possibility of thyroid disorder must be entertained. In particular hypothyroidism must be confirmed or excluded since an affected baby will be condemned to neurodevelopmental handicap.

On trying to explain the abnormalities of thyroid function in the studied babies we postulate that the most likely mechanism of involvement of the thyroid gland is through the direct effect of SARS-CoV-2 on the fetal and neonatal gland. When SARS-CoV-2 is transmitted from the mother to the fetus, the thyroid gland can be affected because of abundance of ACE2 receptors in the gland parenchyma. This action will decrease the thyroid hormone production in the fetal thyroid which will initiate a feedback mechanism leading to excessive secretion of thyroid-stimulating hormone by the fetal pituitary gland and this is reflected in the high TSH levels seen after birth. This fetal primary thyroid hypofunction can be compared to what is seen in babies with congenital hypothyroidism where high TSH level is used as a screening test for primary hypothyroidism. When the baby is born the thyroid gland will be released from the direct effect of the virus and the FT4 returns to normal levels at birth. With presence of high TSH levels at birth, the newborn thyroid gland will be stimulated to secrete more thyroxine which is then reflected in the high FT4 levels seen at 48 - 72 hours after birth. The high levels of free thyroxine will induce a negative feedback mechanism allowing the pituitary to stop production of thyroid-stimulating hormone resulting in normalization of the TSH values at 48 - 72 hours. This possibility of direct viral effect on the thyroid gland is supported by reports from adult postmortem examination of COVID-19 patients which found no significant abnormalities in thyroid follicular morphology [10].

We do not think that the high levels of TSH and FT4 in our babies can be explained by the non-thyroidal illness syndrome (NTIS) or systemic hyperinflammatory state because these babies were clinically normal and stable and had no evidence of inflammatory changes. Furthermore, the reported abnormalities in NTIS are those of low TSH, FT4 and FT3.

As cited above secondary injury by the virus on adult hypothalamic-pituitary-thyroid axis produces central hypothyroidism. However, the situation is different in the perinatal period because maternal or embryonic thyrotropin-releasing hormone (TRH) is not required for normal development of fetal pituitary thyrotrophs. TRH deficient mice are not hypothyroid at birth. In fact, TRH is required later for postnatal maintenance of normal thyrotrophic function [11]. Because of lack of fetal TRH effect on fetal pituitary, it will not be able to stimulate the production of TSH. On the other hand, an injury on the pituitary gland is expected to depress its functions and result in secondary hypothyroidism with normal or low TSH values. Thus, the high levels of TSH and FT4 in our babies cannot be explained by the hypothalamic-pituitary-thyroid axis dysfunction.

Finally follow up for our babies did not reveal temporary or permanent thyroid dysfunction following maternal COVID-19 infection in pregnancy.

Conclusion

COVID-19 infection in pregnancy tends to affect the fetuses and newborns resulting in abnormal thyroid function tests. These abnormalities seem to be related to the direct viral attack on the thyroid gland. However, these abnormal thyroid function tests were transient and were not associated with other morbidities.

Key Clinical Message

COVID-19 in pregnant mothers tends to directly affect the fetal and neonatal thyroid glands. Thyroid function tests (TSH and FT4) should be performed in newborns of COVID-19 mothers and followed to confirm or rule out neonatal thyroid disorders.

Data Availability Statement

All the data used in this study are available from the corresponding author on request and can be found in ClinicalTrial.gov ID NCT 05385029.

Author Contributions

Dr Al Sean Amal: Collection of maternal and newborn data.

Dr Afifi Elham: Collection of maternal and newborn data.

Dr Mutairi Waad: Collection of maternal and newborn data.

Dr Al Hussein Khalid: Supervision of data and provision for analysis.

Dr Miqdad Abeer: Review of COVID-19 literature.

Dr Samadi Abdelmohsen: Supervision of tables and figures.

Dr Alshareef Faisal: Review of the endocrine involvement in COVID-19 and writing manuscript.

Dr Abdelbasit Omer: Writing and revision of the manuscript plus submission.

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Conflicts of Interest

The authors have no conflicts of interest.

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