

# Anosmia, a Hidden Sign for COVID-19? A Case Report and Literature Review

## Case Report

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### ABSTRACT

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic that is actively affecting 210 countries worldwide. Anosmia has been previously reported anecdotally as an emerging symptom of the COVID-19 and only gained recognition as a symptom for COVID-19 by the World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) later on in the pandemic. This case report highlights a case of isolated sudden onset of anosmia as a presenting symptom of COVID-19 and relevant literature review supporting the incidence of anosmia in COVID-19. This is a first case report of anosmia in COVID-19 occurring in pregnancy. A 30-year-old pregnant lady at 11 weeks of gestation presented with sudden onset of anosmia for one day with no other accompanying symptoms. She had just recovered from a mild cold a day prior to the development of anosmia. She had a history of travel by land to Singapore 14 days prior to onset of anosmia. There was no known close contact with a COVID-19 patient or attended any mass gatherings prior to development of her symptom. She underwent nasopharyngeal and oropharyngeal swab sampling which was then tested using reverse transcription polymerase chain reaction (RT-PCR) method and confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinicians should be aware of anosmia as a presenting symptom of COVID-19 especially in the presence of risk factors such as travel to affected countries and having close contact with COVID-19 positive patients and must always adhere to infection control and prevention protocol.

**Key Words:** Anosmia, COVID-19, pandemic, pregnancy, SARS-CoV-2.

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has taken the lives of more than 530 000 people globally<sup>[1]</sup>. The transmission of disease has increased exponentially across many countries within a very brief period. WHO and CDC has recommended that testing for COVID-19 be done for patients who presented with fever, cough, dyspnea or other symptoms compatible to COVID-19 with relevant epidemiological factors under the sound judgement of clinicians<sup>[2, 3]</sup>.

Recently, olfactory dysfunction such as hyposmia and anosmia in the absence of other symptoms has been highlighted as an emerging symptom among COVID-19 positive patients and statements have been released by several otorhinolaryngology societies<sup>[4, 5]</sup>. This symptom however was initially not recognized by the WHO or CDC as a symptom of COVID-19 until later in the pandemic. The intent of this case report is to generate awareness

among the public and clinicians regarding the possibility of anosmia as a silent marker of COVID-19 and to prompt the international scientific community to consider this clinical manifestation in the current case testing and management guidelines while awaiting more vigorous evidence.

This case report highlights a case of isolated sudden onset of anosmia as a presenting symptom of COVID-19 and relevant literature review supporting the incidence of anosmia in COVID-19. This is a first case report of anosmia in COVID-19 occurring in pregnancy.

### Case presentation

A 30-year-old, gravida 1 lady at 11 weeks of gestation visited the antenatal care clinic at a private hospital for her routine check-up. However, she complained of having sudden onset of anosmia on the day of presentation to the antenatal care clinic. Two days prior, she had fever, mild runny nose and non-productive cough which resolved a day before the development of anosmia. On the day of onset of anosmia, she did not have any fever, cough, runny

nose, nasal congestion, shortness of breath, sore throat, vomiting, diarrhea, myalgia, abdominal pain or fatigue. She had no other comorbidities.

She had a history of travel by land in her own vehicle from Johor, Malaysia to Singapore and returned to Johor on the same day 14 days prior to development of anosmia. Her timeline of travel and symptomatology are as in Figure 1. She had no close contact with any known COVID-19 positive patients or attended any mass gatherings prior to development of her symptoms. She lives with her husband who was well.

Upon examination, she was afebrile with normal blood pressure, pulse, respiratory rate and oxygen saturation under room air. She was comfortable and did not appear to be in respiratory distress. Her lung auscultation was clear. No tests for anosmia or blood taking was done. She underwent nasopharyngeal and oropharyngeal swab sampling immediately after consultation at the facility which was then tested using reverse transcription polymerase chain reaction (RT-PCR) method. Healthcare workers attending her wore adequate personal protective equipment (PPE) and adhered to infection control protocol.

As per local guidelines, her symptoms did not fulfil the criteria for being a person under investigation (PUI)<sup>[5]</sup>. Thus, she was allowed discharge from the facility with advice for home surveillance.

After approximately 48 hours, her RT-PCR results confirmed the SARS-CoV-2 infection. She was then referred and admitted to the designated COVID-19 hospital for further management. None of the healthcare workers who had contact with her prior to testing developed any COVID-19 symptoms or anosmia up to date. Her husband was tested negative. She was observed in the hospital, then was allowed discharged after three days when her repeated RT-PCR was negative for COVID-19. Her anosmia completely resolved after six days from onset.



**Fig. 1:** Patient’s timeline from history of travel to development and resolution of anosmia

## DISCUSSION AND CONCLUSION

The current symptoms for suspicion of COVID-19 as outlined by WHO and CDC varies but most have fever, cough, fatigue, shortness of breath, myalgia and other non-specific symptoms such as nasal congestion, sore throat, headache, diarrhea, nausea and vomiting<sup>[1,3]</sup>.

Olfactory dysfunctions such as anosmia and hyposmia as a symptom of COVID-19 on the other hand has been previously only anecdotally reported and described by few studies. The British Rhinological Society, American Academy of Otolaryngology-Head and Neck Surgery and the French Society of Otorhinolaryngology issued expert statements suggesting that anosmia could be a potential feature of COVID-19<sup>[4, 5, 6]</sup>. It was not until later in May 2020 that WHO and CDC recognized olfactory dysfunction as a symptom of COVID-19<sup>[1,3]</sup>. A few studies have been conducted which provides support for anosmia as a presenting symptom of COVID-19. The limitations of these studies are mostly due to the state of emergency of the disease, including some not being peer-reviewed, use of unvalidated questionnaires as well as lack of verification of symptoms by clinical examinations. Findings of the relevant studies are as summarized in (Table 1).

**Table 1:** Summary of literature review

Author	Number of participants	Country	COVID-19 status	Method of anosmia evaluation	Findings relevant to anosmia/hyposmia
Mao <i>et al.</i> , 2020 <sup>[7]</sup>	214	Wuhan	Positive	<ul style="list-style-type: none"> <li>Medical records based on evaluation from two neurologists</li> </ul>	<ul style="list-style-type: none"> <li>11 out of 214 patients (5.1%) had hyposmia</li> <li>3 were severe cases, 8 not severe</li> <li>Finding was not significant (<math>p=0.338</math>)</li> </ul>
Vaira <i>et al.</i> , 2020 <sup>[8]</sup>	320	Italy	Positive	<ul style="list-style-type: none"> <li>Based on history taking and physical examination (no mention of specific tests used)</li> </ul>	<ul style="list-style-type: none"> <li>Estimated that chemosensory dysfunction is present in 19.4%</li> <li>No true statistical data due to state of health crisis in country</li> </ul>
Giacomelli <i>et al.</i> , 2020 <sup>[9]</sup>	59	Italy	Positive	<ul style="list-style-type: none"> <li>Self-reported through questionnaire via verbal interview</li> </ul>	<ul style="list-style-type: none"> <li>20 (33.9%) had at least one taste or olfactory disorder and 11 (18.6%) had both.</li> <li>12 patients had the symptoms prior to hospitalization while 8 of them started experiencing the symptoms during the hospital stay.</li> <li>Females reported these symptoms more frequently than males [10 out of 19 females (52.6%); 10 out of 40 males (25%); <math>p=0.036</math>]</li> </ul>
Lechien <i>et al.</i> , 2020 <sup>[10]</sup>	417	12 European hospitals (Belgium, France, Italy, Spain)	Positive	<ul style="list-style-type: none"> <li>Self-reported through consultation or online questionnaire</li> </ul>	<ul style="list-style-type: none"> <li>357 patients (85.6%) had olfactory dysfunction.</li> <li>Anosmia was present in 284 patients (79.6%) while hyposmia was present in 72 patients (20.4%).</li> <li>Females were found to be more affected by anosmia or hyposmia than males.</li> <li>72.6% regained olfactory function within the first 8 days following disease resolution</li> </ul>
Bagheri <i>et al.</i> , 2020 <sup>[11]</sup>	10069	Iran	Uncertain -the study enrolled all with hyposmia/anosmia within 1-month (since the start of COVID-19 epidemic in Iran) No information provided if they were then tested	<ul style="list-style-type: none"> <li>Self-reported through online questionnaire</li> </ul>	<ul style="list-style-type: none"> <li>There was a surge of olfactory dysfunction coinciding with the COVID-19 epidemic in Iran</li> <li>The correlation between anosmia with the number of COVID-19 positive patients was significant (Spearman correlation coefficient 0.87; <math>p &lt; 0.001</math>)</li> <li>The onset of anosmia was sudden in 76.24%</li> <li>83.38% had decreased taste sensation in association with anosmia.</li> </ul>

Menni <i>et al.</i> , 2020 <sup>[12]</sup>	1 573 103	United Kingdom	Only 1702 tested, 579 were positive, 1123 negative	<ul style="list-style-type: none"> <li>• Self-reported through questionnaire via mobile application</li> </ul>	<ul style="list-style-type: none"> <li>• Loss of smell and taste was reported in 59% of the those tested positive and 18% of those tested negative (OR 6.59; 95% CI 5.25 to 8.27; <math>p=1.9 \times 10^{-39}</math>)</li> <li>• Combination of loss of smell and taste, fever, persistent cough, fatigue, diarrhea, abdominal pain and loss of appetite is predictive of COVID-19 positive test with sensitivity 0.54, specificity 0.86</li> <li>• 40% of COVID-19 patients were anosmic (<math>p &lt; 0.001</math>).</li> <li>• Sniffin test was more sensitive in detecting anosmia in comparison to self-reporting</li> <li>• Not all patients had returned to normal ability to smell 15 days after the start of the first symptoms, although no other symptoms persisted</li> </ul>
Hornuss D <i>et al.</i> , 2020 <sup>[13]</sup>	90	Germany	45 positive, 45 were control	<ul style="list-style-type: none"> <li>• Sniffin test and self-reported via consultation</li> </ul>	<ul style="list-style-type: none"> <li>• 35% of patients in the COVID-19 cohort had smell/taste abnormalities while 0% in the matched controls had these symptoms</li> <li>• COVID-19 patients had significantly lower UPSIT scores</li> </ul>
Moein <i>et al.</i> , 2020 <sup>[14]</sup>	120	Iran	60 positive, 60 control	<ul style="list-style-type: none"> <li>• UPSIT</li> </ul>	<ul style="list-style-type: none"> <li>• Anosmia was reported in 68% (40/59) of COVID-19-positive subjects, compared to 16% (33/203) of COVID-19-negative patients (<math>p &lt; 0.001</math>)</li> </ul>
Yan <i>et al.</i> , 2020 <sup>[15]</sup>	1480	USA	102 positive, 1378 negative	<ul style="list-style-type: none"> <li>• Self-reported via internet-based platform</li> </ul>	<ul style="list-style-type: none"> <li>• Anosmia was independently and strongly associated with COVID-19 positivity (adjusted odds ratio 10.9; 95% CI, 5.08-23.5)</li> </ul>
Kaye <i>et al.</i> , 2020 <sup>[16]</sup>	237	USA, Mexico, Italy, UK, and others	Positive	<ul style="list-style-type: none"> <li>• COVID-19 Anosmia reporting tool for clinicians</li> </ul>	<ul style="list-style-type: none"> <li>• Anosmia was present in 73% of patient prior to COVID-19 diagnosis</li> <li>• Anosmia was the initial symptom in 26.2%</li> <li>• Mean time to anosmia improvement was 7.2 days with 85% of the group within 10 days</li> </ul>
Levinson <i>et al.</i> , 2020 <sup>[17]</sup>	42	Israel	Positive	<ul style="list-style-type: none"> <li>• Questionnaire via mobile phone or email followed by a phone interview upon discharge</li> </ul>	<ul style="list-style-type: none"> <li>• 35.7% patients had anosmia</li> <li>• Median days of of anosmia onset was 3.3 days after illness onset</li> <li>• Median duration of anosmia was 7.6 days</li> <li>• Anosmia was more frequent in those with sore throat (<math>p=0.005</math>) and dyspnea (<math>p=0.02</math>)</li> </ul>

To date, within the limitations of our search, there were very few case reports published regarding sudden onset anosmia who were then confirmed to have COVID-19 by RT-PCR testing. A summary of

the case reports is presented in (Table 2). There were no published case reports retrieved regarding anosmia among COVID-19 positive pregnant patients.

**Table 2:** Summary of case reports

Literature	Age (years)	Sex	Onset of anosmia	Duration of anosmia prior to presentation	Other symptoms	Method of anosmia evaluation	Comorbidities	PCR testing for COVID-19	Resolution of anosmia
Gane <i>et al.</i> , (29 March 2020) <sup>[18]</sup>	45	Male	Sudden	72 hours	None	Self-reported via telephone consultation	None	Positive	Unknown
Villalba <i>et al.</i> , (1 April 2020) <sup>[19]</sup>	85	Male	Sudden	4 days	Fatigue	Self-reported	Hypertension, Ischaemic heart disease and Diabetes Mellitus type II	Positive	Died
Villalba <i>et al.</i> , (1 April 2020) <sup>[19]</sup>	80	Female	Unknown	5 days	Ageusia, fatigue	Self-reported	Hypertension, heart failure and end stage renal failure	Positive	Unknown
Lechner <i>et al.</i> , (3 May 2020) <sup>[20]</sup>	43	Male	Unknown	7 days	Runny nose, mild bilateral nasal obstruction	UPSIT score 25	Smoker 5 sticks/day, history of gastric sleeve operation and hernia repair	Positive	Unknown
Lechner <i>et al.</i> , (3 May 2020) <sup>[20]</sup>	37	Male	Unknown	5 days	Metallic smell and taste, myalgia, recurrent fever, runny nose	UPSIT score 28	History of septoplasty, thoracotomy and pleurectomy of right lung due to spontaneous pneumothorax, right eye toxoplasmosis	Positive	Unknown
Lechner <i>et al.</i> , (3 May 2020) <sup>[20]</sup>	53	Male	Unknown	2 days	Flu like symptoms, tired	UPSIT score 34	-	-	Recovered

The incidence of anosmia correlated with the incidence of COVID-19 as highlighted by the studies in Table 1. Presence of anosmia was associated with other symptoms such as loss of taste, fever, cough, fatigue, runny nose, diarrhea, abdominal pain, loss of appetite, sore throat and dysnea<sup>[12, 17, 19, 20]</sup>. On contrary, 26.2% of the COVID-19 patients had anosmia as the only presenting symptom as reported in the study by Kaye *et al.*, and highlighted by a case report by Gane *et al.*<sup>[16, 18]</sup>

The cause of anosmia in COVID-19 is yet to be ascertained. Nasal endoscopy still possesses a high risk to doctors during this pandemic and deferment of the procedure has been recommended. It has been hypothesized that anosmia could be due to an insult occurring at the neuro epithelium of the olfactory receptor cells in the nasal roof or central olfactory routes<sup>[7, 21]</sup>. A study investigating human and mouse data sets found that olfactory epithelial support cells, stem cells and nasal respiratory epithelium cells expresses the two key genes, angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) which enables proteins production. These proteins then enable the attachment of SARS-CoV-2 onto cells<sup>[21]</sup>. This discovery evokes a probable mechanism of anosmia in COVID-19 and warrants further research for validation.

Most of the studies (Table 2) only ascertained the presence of anosmia via history taking and questionnaires. Only two studies used objective testing using Sniffin test<sup>[13]</sup> and University of Pennsylvania Smell Identification Test Score (UPSIT)<sup>[14]</sup>. The percentage of anosmia among the COVID-19 cohort was 40% with the Sniffin test and 35% with UPSIT. The mean UPSIT score was 20.98 and 25% were anosmic, 33% severely microsmic, 27% moderate microsmia, 13% mild microsmia and 2% had normosmia<sup>[14]</sup>.

Due to the nature of the pandemic, follow up times were brief, but it has been observed that anosmia resolves within one to two weeks as COVID-19 infection improves. Kaye *et al.*, reported that the mean time to improvement was 7.2 days and 85% of the cohort within 10 days while Levinson *et al.*, found that the median duration to anosmia resolution was 7.6 days<sup>[16, 17]</sup>

In relation to our case, the symptoms of COVID-19 in pregnancy has been reported to be similar with the non-pregnant adults which are fever, sore throat, malaise, dyspnea and cough<sup>[22]</sup>. The COVID-19 severity is also equivalent to the non-pregnant population with the majority cases being mild<sup>[23]</sup>. There are currently no data suggesting an increased risk of miscarriage or early pregnancy loss however, those who develop

pneumonia were found to have a higher incidence of preterm labour, preterm birth, prelabour rupture of membranes, pre-eclampsia and caesarean delivery for abnormal fetal heart tracings<sup>[24]</sup>. Vertical transmission of COVID-19 is yet to be established but studies have shown that samples of amniotic fluid, cord blood, breastmilk and neonatal throat swabs were negative for SAR-CoV-2<sup>[25]</sup>. As of time of this writing, there are no reported cases of maternal death due to COVID-19.

The patient in our case has been allowed discharge from the COVID-19 designated hospital after her repeated RT PCR after 72 hours was negative and achieved complete resolution of anosmia after six days from onset. She did not develop any respiratory distress or experienced any signs of miscarriage or pregnancy loss. She has been advised for home quarantine for 14 days. She was pleased that the attending physician who first saw her was aware of anosmia being a probable symptom of COVID-19 and tested her despite not fulfilling the national criteria for testing<sup>[26]</sup>. She is thankful that COVID-19 was promptly detected, and she was referred for further management by a multidisciplinary team.

COVID-19 is still a very new, challenging disease and research gaps are still present. Future studies might want to consider exploring the anosmia predilection towards females, it's recovery as well as treatment modalities.

## CONCLUSION

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Globally, most countries are yet to begin testing patients with complaints of anosmia for COVID-19. These patients with isolated anosmia could represent the submerged part of the COVID-19 iceberg as they might be vectors of the virus. However, up to date, the sensitivity, specificity, and predictive value of anosmia as a predictor of COVID-19 is still undetermined. Additionally, a universal definition of anosmia together with recommendations of olfactory dysfunction evaluation and management during this pandemic should be proposed. This would enable comparisons of evidence to be made and strong conclusions drawn regarding anosmia in COVID-19 to guide clinicians and researchers.

## LIST OF ABBREVIATIONS

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COVID-19: coronavirus disease 2019

UPSIT: University of Pennsylvania Smell Identification Test score

WHO: World Health Organization

CDC: Centre for Disease Control and Prevention

RT-PCR: reverse transcription polymerase chain reaction

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PPE: personal protective equipment

PUI: person under investigation

ACE2: angiotensin converting enzyme 2

TMPRSS2: and transmembrane serine protease 2

## CONFLICT OF INTEREST

There are no conflicts of interest.

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