EUROX 21 (2024) 100270

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

How does the need for IVF affect pregnancy complications among multiple gestations? The study of a large American population database including almost 100,000 multiple gestations

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ARTICLE INFO

Keywords:
In vitro fertilization (IVF)
Assisted reproductive technology
Multifetal pregnancies
Multiple pregnancies
Pregnancy complications

ABSTRACT

Objective: This study's aim is to compare pregnancy outcomes in multifetal gestations that were conceived spontaneously compared to in vitro fertilization (IVF). Few population-based studies have addressed this topic.
Study design: This is a retrospective cohort study using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database. Our study cohort included 90,552 multifetal gestations conceived spontaneously and 3219 IVF conceptions, from 2008 to 2014, inclusively. Multivariate logistic regression analyses were performed comparing maternal and neonatal outcomes, whilst adjusting for confounding variables. Subject was conducted using ICD-9 codes for multifetal gestation: 651. X and 76.1 and ICD-9 code for IVF: 23.85. Each pregnancy was included once.
Results and conclusion: IVF multifetal gestations had increased risk of pregnancy-induced hypertension (aOR 1.31, 95 % CI 1.20–1.43), gestational hypertension (aOR 1.21, 95 % CI 1.04–1.41), preeclampsia (aOR 1.31, 95 % CI 1.19–1.45), gestational diabetes (aOR 1.26, 95 % CI 1.13–1.41) and placenta previa (aOR 1.7, 95 % CI 1.32–2.19). IVF delivery outcomes were more likely complicated by cesarean section (aOR 1.21, 95 % CI 1.10–1.33), preterm premature rupture of membranes (aOR 1.33, 95 % CI 1.16–1.52), chorioamnionitis (aOR 1.71, 95 % CI 1.37–2.14), postpartum hemorrhage (aOR 1.44, 95 % CI 1.26–1.63) and transfusions (aOR 1.48, 95 %CI 1.26–1.74). IVF neonatal outcomes were more likely complicated by small for gestational age (aOR 1.26, 95 % CI 1.12–1.41) and congenital anomalies (aOR 1.82, 95 % CI 1.29–2.57). IVF was not found to increase risks of eclampsia, preterm delivery, operative vaginal delivery, hysterectomy, or intrauterine fetal demise.
IVF increased the risk of pregnancy, delivery, and neonatal outcomes in multifetal pregnancies with risks increased from 20 % to 70 %. The role of infertility versus the need for IVF and the type of IVF protocol used should be further evaluated.

1. Introduction

Assisted reproductive technology (ART) constitutes approximately 1.9 % and 4.5 % of yearly births in the United States of America and Europe, respectively [1,2]. Delayed family planning has resulted in an increase in ART use. IVF constitutes a risk for multifetal pregnancy; however, increased adoption of single embryo transfer has decreased this risk [3–6]. Multiple embryo transfer occurs commonly in older women with a resultant increase in multiple pregnancies [7,8]. Single blastocyst transfer also leads to higher twin rates, presumably due to laboratory manipulation [9]. Multifetal gestations when compared to singleton gestations are at an increased risk of hyperemesis gravidarum, gestational diabetes mellitus, pregnancy-induced hypertension, anemia, hemorrhage, cesarean section and postpartum depression [4,10,11]. Multifetal gestations have also been found to increase fetal growth restriction and preterm birth [10,11]. A retrospective cohort study done in China (Wang et al., 2021) found that within IVF, twin pregnancies and maternal age were independently associated with adverse obstetric outcomes [7]. However, few studies have addressed the risks of IVF multifetal gestations in a population database, and no studies have

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https://doi.org/10.1016/j.eurox.2023.100270
Received 25 April 2023; Received in revised form 25 November 2023; Accepted 8 December 2023
Available online 9 December 2023

evaluated these risks in North America where IVF stimulation is carried out differently than in Europe, Asia or Africa [12–16]. It should be noted that pregnant patients in North America are expected to have greater risks of obesity and different rates of smoking and possibly illicit drug use [17–19]. As such, it may be expected that IVF in North America would be associated with a different set of risks. Therefore, this study aimed to evaluate the risk of multifetal gestations conceived after IVF as compared to spontaneous multifetal gestations. A large population database was utilized for this purpose.

2. Materials and methods

We conducted a retrospective population-based study utilizing data from the healthcare cost and utilization project-Nationwide Inpatient Sample. (HCUP- NIS) from 2008 to 2014, inclusively. The data from 2014 onwards was not extracted due to the difference in the coding system, because it uses the international classification of diseases, tenth edition (ICD- 10) as opposed to ICD- 9 which was used from 2008 to 2014 and which is not comparable. The HCUP-NIS is the largest inpatient sample database in the USA and consists of hospital inpatient stays in 49 states and the District of Columbia. Each year, the database provides information relating to seven million inpatient stays, including patient characteristics, diagnoses, and procedures. The data is representative of ~ 20 % of hospital admissions and geographically represents ~ 96 % of the American population.

We evaluated deliveries, by using the ICD-9 clinical modification (ICD-9-CM) codes for delivery-related discharge diagnoses (650.xx, 677. xx, 651.xx-676.xx where the fifth digit is 0, 1, or 2), and birth-related procedural diagnosis (72.x, 73.x, 74.0–74.2). We limited our study group to admissions that ended in delivery or maternal death to guarantee that multiple admissions in the same pregnancy were excluded. Among this group, we evaluated multifetal gestations using ICD-9 codes 651. X and 761.5. A subdivision of this group was conducted to identify pregnancies conceived through IVF using ICD-9 procedural code 23.85. Those spontaneously conceived multifetal gestations were the control group.

Maternal demographic and baseline characteristics, and pregnancy, delivery and neonatal outcomes were identified using the appropriate ICD-9 codes. Demographic characteristics included age, race, income quartiles and insurance type. Maternal characteristics included obesity (body mass index $\geq$ 30 kg/m^2), previous cesarean, smoking and illicit drug use during pregnancy, chronic hypertension, pregestational diabetes mellitus and thyroid disease.

Pregnancy outcomes evaluated were gestation diabetes, placenta previa and pregnancy-induced hypertension, including gestational hypertension, preeclampsia, eclampsia, and hypertension superimposed with preeclampsia or eclampsia. Delivery outcomes included were preterm premature rupture of membranes (PPROM), preterm birth, abruptio placenta, vaginal delivery, operative vaginal delivery, cesarean section, chorioamnionitis, hysterectomy, postpartum hemorrhage (PPH), wound complications defined as partial or complete wound separation, blood transfusion, maternal death, disseminated intravascular coagulation, maternal infection, and venous thromboembolism. Maternal infections were composed of septicemia during labor, postpartum endometritis, septic pelvic thrombophlebitis, or peritonitis. Venous thromboembolism included deep vein thrombosis and pulmonary embolism antenatal, intrapartum, or postpartum. Neonatal outcomes included were small for gestational age (SGA) defined $\leq$ 10 % for weight at the gestational age of birth, intrauterine fetal demise (IUFD) and congenital anomalies.

3. Statistical analysis

An initial analysis was performed to identify the prevalence of multifetal gestations conceived yearly spontaneously and through IVF. Chi-squared tests were used to compare baseline demographic and clinical characteristics of women who underwent IVF and those who did not. Subsequently, univariate, and multivariate logistic regression analyses were conducted to explore associations between IVF and maternal, delivery and neonatal outcomes through calculation of the odds ratios (OR) and 95 % confidence intervals (CI). The regression models were adjusted for the potential confounding effects of maternal demographic and preexisting clinical characteristics and presented as adjusted odds ratios (aOR) for pregnancy outcomes. Delivery, other and neonatal outcomes were adjusted for the previous confounding factors in addition to statistically significant pregnancy outcomes. All analyses were performed using SPSS 25.0 (IBM Corporation, Chicago, IL, USA) software. Per convention, if one outcome occurs in five or fewer cases, the N was put in the respective table and the data was considered unreliable.

This study used exclusively publicly accessible, anonymized data; therefore, according to articles 2.2 and 2.4 of the Tri-Council Policy Statement (2010), institutional review board approval was not required.

4. Results

A total of 93,771 multifetal gestations were included. Of these, 3219 were conceived through IVF. Baseline maternal demographic and clinical characteristics are summarized in Table 1. Women who underwent IVF were more likely to be $\geq$ 35 years old, be Caucasian, Asian or Pacific islanders, have an income of $\geq$ $ 63,000, and have private health insurance ($p < 0.0001$). Women who conceived through IVF had a higher prevalence of thyroid disease, 14.1 % vs. 5.2 % ($p < 0.0001$). On the other hand, women who conceived a multifetal pregnancy spontaneously were more likely to be obese (6.3 % vs. 5.3 %, $p < 0.024$), have a history of previous cesarean (15.7 % vs. 11.2 %, $p < 0.0001$), and history of smoking (4.7 % vs. 0.4 %, $p < 0.0001$) or illicit drug use during pregnancy (1.3 % vs. 0.1 %, $p < 0.0001$).

After adjusting for the above-mentioned confounding factors (Table 2), IVF multifetal gestations were found more likely to be complicated by pregnancy-induced hypertension (aOR 1.31, 95 % CI 1.20–1.43), gestational hypertension (aOR 1.21, 95 % CI 1.04–1.41), preeclampsia (aOR 1.31, 95 % CI 1.19–1.45), gestational diabetes (aOR 1.22, 95 % CI 1.13–1.41), and placenta previa (aOR 1.70, 95 % CI 1.32–2.19).

The association between IVF pregnancy and delivery outcomes is also shown in (Table 2). IVF pregnancies had a greater likelihood of being complicated by PPROM (aOR 1.33, 95 % CI 1.16–1.52), chorioamnionitis (aOR 1.71, 95 % CI 1.37–2.14), PPH (aOR 1.44, 95 % CI 1.26–1.63), requiring a blood transfusion (aOR 1.48, 95 % CI 1.26–1.74), maternal infection (aOR 1.60, 95 % CI 1.32–1.96), and delivery by cesarean (aOR 1.21, 95 % CI 1.10–1.33). Spontaneous multifetal pregnancies were more likely to result in a vaginal delivery (aOR 0.84, 95 % CI 0.76–0.93). Other outcomes including preterm birth, abruptio placenta, operative vaginal delivery, hysterectomy, and maternal death were not found to be statistically different between the two groups. As summarized in Table 3, twins conceived through IVF were more likely to be SGA (aOR 1.26, 95 % CI 1.12–1.41) and have a higher risk of congenital anomalies (aOR 1.82, 95 % CI 1.29–2.57). Multifetal IVF pregnancies were not found to be associated with an increased risk of IUFD as compared to spontaneously conceived multifetal pregnancies.

5. Discussion

The study's objective was to evaluate pregnancy, delivery and neonatal outcomes in IVF multifetal gestations compared to spontaneously conceived gestations based on a large population-sized American database.

In this study, we have found that IVF multifetal pregnancies were more likely complicated by pregnancy-induced hypertension, gestational hypertension, preeclampsia, gestational diabetes, and placenta previa. Additionally, women who underwent IVF were more likely to be

Table 1
Maternal characteristics.

Characteristics	IVF* N = 3219 %	No IVF N = 90,552 %	P-value
Maternal Age (years)			< 0.0001
< 25	1.8	24	
	N = 59	N = 21,937	
25–34	45	53	
	N = 1458	N = 47,808	
≥ 35	53	23	
	N = 1702	N = 20,796	
Race			< 0.0001
White	71	59	
	N = 2151	N = 47,232	
Black	6.7	16	
	N = 202	N = 13,132	
Hispanic	6.3	15	
	N = 191	N = 12,181	
Asian and Pacific	10	4.6	
	N = 309	N = 3740	
Other	0.6	0.7	
	N = 17	N = 528	
Other	5.5	4.6	
	N = 166	N = 3679	
Income quartiles			< 0.0001
Less than 39,000	6.5	24	
	N = 209	N = 21,132	
$39,000–47,999	13	23	
	N = 419	N = 20,432	
$48,000–62,999	26	25	
	N = 820	N = 22,387	
$63,000 or more	55	28	
	N = 1745	N = 25,308	
Insurance plan type			< 0.0001
Medicare	0.1	0.7	
	N = 3	N = 641	
Medicaid	4.0	34	
	N = 129	N = 30,783	
Private including HMO	93	60	
	N = 2992	N = 54,437	
self-pay	1.4	2.0	
	N = 45	N = 1805	
Obesity	5.3	6.3	0.02
	N = 172	N = 5730	
Previous Cesarean	11	16	< 0.0001
	N = 363	N = 14,224	
Smoking during pregnancy	0.4	4.7	< 0.0001
	N = 12	N = 4278	
Chronic HTN	3.2	3.2	0.88
	N = 2881	N = 104	
Pregestational Diabetes	1.0	1.0	0.96
	N = 33	N = 921	
Illicit Drug use	0.1	1.3	< 0.0001
	N = 3	N = 1143	
Thyroid disease	14	5.2	< 0.0001
	N = 453	N = 4737	

IVF: In vitro fertilization, HTN: Hypertension, HMO: Health maintenance organization.

older which makes initiative sense because this group is more likely to be infertile and have multiple embryos transferred. Both increasing maternal age and IVF are reported to be linked with increased risk for pregnancy-induced hypertension. We controlled for age in our analysis and still found this risk to be increased. This augmented risk of pregnancy-induced hypertension was also found in IVF singleton pregnancies as shown by Pandey and coauthors in their meta-analysis and systematic review [20].

This may be due to the hyperestrogenic state induced during IVF associated with endothelial dysfunction [21]. Thus leading to abnormal placentation and an increased risk of hypertension. It is theorized that the hormonal milieu during IVF compared to that in spontaneous pregnancy along with the preexisting underlying metabolic-vascular state of patients undergoing IVF may play a role in the development of gestational diabetes and hypertension [21]. Embryo transfer and embryo culture affect implantation and embryo development; thus, abnormal placentation such as placenta previa can occur. This is hypothesized to be a result of uterine contractions caused by the embryo transfer via the trans-cervical catheter, which can result in mechanical stimulation of the internal os and thus release of prostaglandins [22,23].

The risk of PPH is increased in multifetal gestations [24]. Our study has shown that IVF multifetal gestations are at increased risk of PPH when compared to spontaneous multifetal gestations. This increased risk has been shown previously to exist with IVF singleton pregnancies [20].

Congenital anomalies were also more likely to occur and probably share the same pathophysiology as IVF singleton pregnancy. A meta-analysis comparing rates of birth defects in singleton pregnancies conceived through ART vs. natural conception found that neonates born after ART had a higher risk [25]. They postulated this may be due to characteristics of the infertile couple or the process of IVF such as ovarian hyperstimulation, media culture of the embryo, and the freezing and thawing of the embryo which may affect embryo differentiation through altered methylation and gene expression [24]. Even though multiple pregnancies are known risk factors for congenital anomalies [26] it appears that IVF is additive to this risk, raising the risk substantially by about 80 %.

While the literature is limited on delivery outcomes such as preterm birth and SGA; studies have demonstrated an increased risk in IVF pregnancies [27,28]. This could be hypothesized to be attributed to the IVF cycle characteristic itself or the inherent features of patients who require IVF [27,29]. Again, multifetal pregnancies are known to be risks for preterm birth and SGA. We however found that IVF multifetal pregnancies are further at risk for these complications with the risk increased by 7 % and 26 % respectively [30]. Studies have shown that IVF singleton pregnancies also have an increased risk of SGA when compared to naturally conceived singleton pregnancies [28,20,21]. Furthermore, increased levels of insulin-like growth factor-binding protein levels found in ART pregnancies have been linked to intrauterine growth restriction [22].

A meta-analysis comparing risks of spontaneous preterm birth in singleton pregnancies conceived with IVF or intracytoplasmic sperm injection (ICSI) vs. spontaneously found an increased risk of 80 % in pregnancies conceived through IVF or ICSI [31]. It is also important to keep in mind iatrogenic causes of preterm birth in IVF pregnancies due to abnormal placentation and in some cases may be related to the patient [20,21,32]. On the other hand, we found no statistical difference in preterm birth rates. In our study, delivery outcomes in IVF multifetal gestations were more likely to be complicated by PPROM, chorioamnionitis, PPH, transfusion, maternal infection and cesarean section as compared to spontaneously conceived multiple gestations. These findings remain consistent with published results seen in IVF singleton pregnancies [33]. It should be noted that in our study there were no statistical differences for the outcomes: abruptio placenta, operative vaginal delivery, hysterectomy and maternal death. Some of which is due to the small rate of incidence of these complications; for example, peripartum hysterectomy complicates 1 per 1000 deliveries in the United States. However, in the literature, IVF was found to have an increased risk of preterm birth and perinatal mortality in singleton pregnancies, when meta-analyses were performed [34,35]. Singleton IVF pregnancies demonstrate a higher risk with regard to the associated risk of hysterectomy [36]. This is in contrast to our findings in multifetal IVF pregnancies and is likely related to the increased risks of hysterectomy deliveries in multifetal gestations overshadowing the risk of IVF. The same explanation can be applied to the lack of risk difference with regards to abruptio placenta [37,38].

The increased risk of cesarean seen in IVF multiple gestations may be related to requested cesarean sections and some being hesitant to attempt vaginal delivery in women with advanced maternal age, multiples and IVF. This is similar to findings of other studies looking at IVF multifetal gestations [7]. It is important that future studies attempt to

Table 2
Pregnancy and delivery outcomes.

Outcomes	IVF (%) N = 3, 219	No IVF (%) N = 90, 551	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Adjusted p-value
Pregnancy outcomes[a]					
Pregnancy induced hypertension	25 N = 802	19 N = 16,739	1.46 (1.35–1.59)	1.31 (1.20–1.43)	< 0.0001
Gestational hypertension	6.2 N = 201	5.1 N = 4633	1.24 (1.07–1.43)	1.21 (1.04–1.41)	0.01
Preeclampsia	17 N = 554	12 N = 10,982	1.51 (1.37–1.65)	1.31 (1.19–1.45)	< 0.0001
Eclampsia	0.1 N = 3	0.2 N = 150	0.56 (0.18–1.76)	0.438 (0.11–1.80)	0.25
Hypertension superimposed with preeclampsia or eclampsia	1.8 N = 57	1.4 N = 1260	1.28 (0.98–1.67)	1.22 (0.91–1.63)	0.19
Gestational diabetes	14 N = 435	8.5 N = 770	1.68 (1.52–1.87)	1.26 (1.13–1.41)	< 0.0001
Placenta previa	2.3 N = 74	0.9 N = 834	2.53 (1.99–3.22)	1.70 (1.32–2.19)	< 0.0001
Delivery outcomes[b]					
PPROM	8.1 N = 260	6.3 N = 5713	1.31 (1.15–1.49)	1.33 (1.16–1.52)	< 0.0001
Preterm birth	42 N = 1342	42 N = 38,321	0.97 (0.91–1.05)	1.07 (0.99–1.16)	0.09
Abruptio placenta	2.3 N = 75	2.1 N = 1929	1.10 (0.87–1.39)	1.23 (0.96–1.57)	0.10
Chorioamnionitis	3.0 N = 95	2.0 N = 1805	1.50 (1.21–1.84)	1.71 (1.37–2.14)	< 0.0001
Operative vaginal delivery	4.2 N = 136	5.0 N = 4569	0.83 (0.70–0.99)	0.86 (0.72–1.04)	0.12
Caesarean section	79 N = 2554	74 N = 66,703	1.37 (1.26–1.50)	1.21 (1.10–1.33)	< 0.0001
Spontaneous Vaginal delivery	16 N = 529	21 N = 19,280	0.73 (0.66–0.80)	0.84 (0.76–0.93)	0.001
Hysterectomy	0.4 N = 13	0.3 N = 235	1.56 (0.89–2.72)	1.01 (0.56–1.80)	0.99
Postpartum Haemorrhage	9.9 N = 318	6.2 N = 5647	1.65 (1.46–1.86)	1.44 (1.26–1.63)	< 0.0001
Wound complications	1.6 N = 51	1.0 N = 891	1.62 (1.22–2.15)	1.29 (0.95–1.74)	0.10
Maternal Death	0.0 N = 0	0.0 N = 7	0.000	0.000	0.99
Transfusion	6.0 N = 190	4.4 N = 3957	1.37 (1.18–1.60)	1.48 (1.26–1.74)	< 0.0001
Others[b]					
Maternal infection	3.7 N = 120	2.7 N = 2426	1.41 (1.17–1.70)	1.60 (1.32–1.96)	< 0.0001
Deep vein thrombosis	0.0 N = 1	0.1 N = 79	0.36 (0.05–2.56)	0.26 (0.04–1.90)	0.18
Venous thromboembolism	0.1 N = 4	0.1 N = 119	0.95 (0.35–2.56)	0.73 (0.26–2.02)	0.55
Disseminated intravascular coagulation	1.2 N = 38	0.6 N = 565	1.90 (1.37–2.65)	1.57 (1.11–2.22)	0.01

PPROM: preterm premature rupture of membranes.
a Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use and smoking during pregnancy.
b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa.

address the cause of this difference.

Contrary to our findings of the increased risk of pregnancy-induced hypertension in IVF multifetal pregnancies; a Dutch study by Szymusik et al., comparing a cohort of similar European patients found no increased risk between IVF multiples and spontaneous multiple pregnancies [39]. It is likely this difference is due to the different populations studied and the increased risk of hypertension may be related to the American population. Additionally, where we found an increased risk of SGA in IVF multifetal pregnancies, the Dutch study by Szymusik et al. found no increased risk. It is worth mentioning however that in a subsequent meta-analysis the relative risks of SGA were similar in IVF versus spontaneously conceived multiple pregnancies [40]. The role of geographic location on this finding should also be considered as contributing to the outcomes differences seen.

There are several limitations to this study. To begin with, the reliance on a retrospective database is a known risk for coding errors and undetermined biases, this is a limitation of all large population databases. However, we prefer such types of studies, given the large number of subjects that could be included. In our case, this was approximately 100,000 multiple gestations. Information about infertile subjects with spontaneous conceptions wasn't available, making it impossible to determine whether complications are associated with IVF treatments as opposed to underlying infertility. Moreover, the database does not permit separation of frozen and fresh embryo transfers which may have given different results and complications. Furthermore, it is likely that IVF is under-represented in the database and that some of the multiple gestations that acted as the controls may have had IVF. However, this would only minimize differences between the groups and as such any increases in pregnancy complications in the IVF group are likely true.

Some of the main strengths of this study are that it is the first of its

Table 3
Neonatal outcomes.[b]

Outcomes	IVF (%) n = 3, 219	No IVF (%) n = 90, 551	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Adjusted p-value
SGA	12 N = 387	9.4 N = 8509	1.32 (1.18–1.47)	1.26 (1.12–1.41)	< 0.0001
IUFD	0.6 N = 19	0.8 N = 755	0.71 (0.45–1.12)	0.91 (0.55–1.51)	0.71
Congenital Anomalies	1.2 N = 40	0.6 N = 570	1.99 (1.44–2.74)	1.82 (1.29–2.57)	0.001

SGA: Small for gestational age, IUFD: intrauterine fetal death.
b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa.

kind in North America in addition to including a large number of multifetal gestations.

6. Conclusion

In conclusion, IVF among the American population imposes a higher risk on multifetal gestations. These risks are pregnancy-induced hypertension, gestational hypertension, preeclampsia, gestational diabetes, PPROM, PPH, blood transfusion, placenta previa and others. In addition, neonates from IVF multifetal gestations are more likely to be SGA and at increased risk of congenital anomalies. Hence, healthcare providers should be vigilant about these complications and multifetal gestations in IVF should try to be avoided to mitigate these risks.

CRediT authorship contribution statement

Dahan Michael: Conceptualization, Data curation, Supervision, Writing – review & editing. **Baghlaf Haitham:** Formal analysis, Writing – review & editing. **Badeghiesh Ahmad:** Data curation, Formal analysis, Writing – review & editing. **Mandourah Samar:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

None

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