

ORIGINAL RESEARCH ARTICLE

Obstetric anal sphincter injuries—Maternal, fetal and sociodemographic risk factors: A retrospective register-based study

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Abstract

Introduction: Obstetric anal sphincter injuries (OASIS) are severe complications to vaginal births with potentially serious long-term consequences and large impact on quality of life. The aim was to determine risk and protective factors for OASIS.

Material and methods: We performed a retrospective register-based observational study. A cohort of 988 988 singleton term deliveries 2005–2016 in Sweden were included. Data from the Swedish Medical Birth Registry and Statistics Sweden were extracted to identify cases of OASIS and maternal and fetal characteristics. Modified Poisson Regression analyses were performed to assess risk factors.

Results: The rate of OASIS was 3.5% ($n = 34\,583$). Primiparity (adjusted risk ratio [aRR] 3.13, 95% CI 3.05–3.21), vacuum extraction (aRR 2.79, 95% CI 2.73–2.86), forceps (aRR 4.27, 95% CI 3.86–4.72), and high birthweight (aRR 2.61, 95% CI 2.50–2.72) were associated with a significantly increased risk of OASIS. Increasing maternal age and decreasing maternal height also increased the risk of OASIS. Obesity increased the risk of OASIS (aRR 1.04, 95% CI 1.04–1.08), if fetal birthweight was not adjusted for. Smoking (aRR 0.74, 95% CI 0.70–0.79) and low maternal education (aRR 0.87, 95% CI 0.83–0.92) were associated with a decreased frequency of reported OASIS. Previous cesarean section increased the risk of OASIS (aRR 1.41, 95% CI 1.36–1.47).

Conclusions: Primiparity, instrumental delivery, and high birthweight significantly increased the risk of OASIS. Obesity, low height, increasing age, and previous cesarean section also increased the risk whereas smoking and low maternal educational level were associated with a lower OASIS rate.

KEYWORDS

labor complications, obstetric delivery, obstetric sphincter injuries, pelvic floor disorder, risk factor

Abbreviations: aRR, adjusted risk ratio; BMI, body mass index; cRR, crude risk ratio; CS, cesarean section; OASIS, obstetric anal sphincter injury; RR, risk ratio; VBAC, vaginal birth after cesarean delivery.

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1 | INTRODUCTION

Obstetric anal sphincter injuries (OASIS) are serious complications to vaginal deliveries. They represent the most significant risk factor for developing female anal incontinence and might also cause perineal pain, dyspareunia, and fecal urgency, leading to significant long-term suffering and potential stigmatization.^{1,2}

Perineal injuries are classified according to a definition published by Sultan.³ First- and second-degree injuries involve the vaginal epithelium and perineal muscles, respectively. OASIS include third- and fourth-degree injuries to the perineum involving the external and internal anal sphincters, and the anal epithelium to varying extents.³

There are several well-established risk factors associated with a higher risk of OASIS, including primiparity, fetal macrosomia, instrumental vaginal delivery, and prolonged second stage of delivery.^{4,5} Several other aspects have been proposed to affect the risk, including maternal age, body mass index (BMI), episiotomy, and smoking, but the evidence has either been sparse or not consistent in published material.⁶⁻⁸

The prevalence of sphincter injury has fluctuated over the last decades and differs between countries. The incidence varies between 0.7% and 4.2% in the Nordic countries.⁹ An increasing trend has been observed where several explanations have been proposed; larger infant size, increase in instrumental deliveries, improved diagnostic accuracy, and changed clinical practice of management of second stage of delivery.^{9,10}

Despite OASIS being recognized as a significant cause of both long- and short-term morbidity there is no international consensus regarding the use of preventive measures. Controlled delivery of the head,¹¹ use of warm compresses,¹² and delivery position¹³ have all been shown to decrease the risk of OASIS. Perineal protection maneuvers have not been proven to have an effect in clinical studies but are used on a routine basis in clinical practice in Sweden and have been part of interventional programs that have successfully reduced the incidence of OASIS.¹⁴

Identifying risk factors to provide optimal care for high-risk women could lead to a significant decrease in long-term suffering. The aim of this nationwide register-based study was therefore to assess maternal and fetal risk and protective factors for OASIS across the Swedish population.

2 | MATERIAL AND METHODS

The study population consisted of 988 988 women with singleton term ($\geq 37^{+0}$) vaginal deliveries in Sweden 2005–2016. The data were extracted from the Swedish Medical Birth Registry, which was founded in 1973 and includes data on almost all deliveries (98%–99%) in Sweden. All healthcare providers are obliged to report to the registry and the system is identical throughout the country. It contains information collected from medical records registered at antenatal visits, delivery units, and initial pediatric examination of

Key message

The risk of obstetric anal sphincter injury is affected by a range of risk factors. Primiparity, instrumental delivery, vaginal birth after cesarean delivery, macrosomia, low height, increasing age, and obesity all appear to increase the risk whereas smoking and low maternal education are associated with decreased risk.

the infant. A detailed quality control and validation of the registry was published in 2003.¹⁵

At the first antenatal visit the women are interviewed by their midwife regarding their pre-pregnancy health, including smoking habits and use of medical drugs. The height and their booking weight are also registered. Maternal BMI was calculated as weight (kg)/(height [m])², and was categorized according to WHO's classification into underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²). Information regarding maternal educational level and maternal country of birth was obtained through linkage with data from Statistics Sweden. Cases of OASIS were identified through checkboxes, or International Classification of Diseases codes O702 and O703 reported to the Medical Birth Registry or the National Patient Registry within 6 weeks of delivery.

2.1 | Statistical analyses

Risk ratios (RR) and adjusted risk ratios (aRR) for sphincter rupture were obtained using modified Poisson Regression analyses (SPSS version 25; IBM). In the first calculation model, adjustments were made for year of delivery (classes 2005–2008, 2009–2012, 2013–2016) and maternal characteristics, including: maternal age (classes <20, 20–24.9, 25–29.9, 30–34.9, 35–39.9, or ≥ 40 years), parity (1, 2, or ≥ 3 children), BMI classes (<18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m², or not known), smoking (yes, no, or not known), maternal height classes (<155, 155–164, 165–174, ≥ 175 cm, or not known), maternal country of birth (Nordic countries, other European countries/USA/Canada/Australia/New Zealand, others, or not known), and maternal educational level (\leq primary/lower secondary [1–9 years], upper secondary [10–12 years], <3 years of higher education, ≥ 3 years of higher education, or not known). In the second calculation model, adjustments for delivery mode (vaginal non-instrumental, vacuum extraction, or forceps) were added to the previously mentioned variables. In the third and final calculation model infant birth-weight (<2500, 2500–2999, 3000–3499, 3500–3999, 4000–4499, ≥ 4500 g) was also added to the adjustments. Findings with *p* values less than 0.05 were regarded as statistically significant. Records with missing data were included, grouped as “not known”, in the analyses.

2.2 | Ethics statement

The study was approved by the Regional Medical Ethics Committee, Lund, Sweden (reference number 2018/538) on August 2, 2018.

3 | RESULTS

Between 2005 and 2016, 988 988 vaginal deliveries were recorded in the Medical Birth Registry. The rate of OASIS was 3.5% ($n = 34\,583$). Table 1 shows maternal characteristics and delivery mode in relation to the crude risk of OASIS. There was an overall 7% decrease of OASIS during 2013–2016 compared with 2005–2008. A total of 846 446 (86%) were complete cases.

Primiparous women were approximately three times as likely to attain OASIS compared with multiparous women, and the strong association between primiparity and OASIS remained after adjustments.

The strongest risk factor for OASIS was instrumental delivery, where the most significant risk increase was seen with the use of forceps (crude risk ratio [cRR] 6.88). The prevalence of vacuum extraction was 8.3% and the use of forceps was rare at 0.2%. Birthweight was also strongly associated with increased risk of OASIS and the risk increased significantly with higher birthweight as seen in Table 2.

The risk of OASIS increased with maternal age as seen after adjusting for maternal characteristics (Table 3), where the highest risk was in the age group 34–39 years, and the lowest risk was among women younger than 20 years. When also adjusting for delivery mode, the association between OASIS and increasing maternal age was less pronounced, albeit still statistically significant.

In the crude model, high BMI ($>30\text{ kg/m}^2$) had a considerably protective effect (cRR 0.80), but after initial adjustment for maternal characteristics and then delivery mode this association disappeared. After also adjusting for birthweight, a negative association was again seen, but less pronounced (aRR 0.90). Low BMI ($<18.5\text{ kg/m}^2$) showed a risk increase of OASIS compared with women with normal BMI (cRR 1.12). Through all three steps of adjustment, the risk increase among women with BMI less than 18.5 kg/m^2 was maintained, and the positive association was even more noticeable (aRR 1.30). Short maternal height showed a positive association with risk of OASIS, which became more evident after adjusting both for maternal characteristics, delivery mode, and birthweight (height $<155\text{ cm}$: aRR 1.72, compared with height $>175\text{ cm}$: aRR 0.82).

Maternal smoking appeared to be negatively associated with risk of OASIS and this association remained after adjusted calculations, even when adjusting for birthweight (aRR 0.74). A correlation between increased risk of OASIS and higher maternal educational level was found, and adjustment for maternal characteristics, delivery mode, and birthweight only marginally altered the risk estimates.

According to the crude estimates, no association between maternal country of birth and OASIS was found, but when adjustments were made, decreased risk (aRR 0.92) was found among women

from Europe/ USA/ Canada/ Australia/ New Zealand compared with women from the Nordic countries, whereas women with other ethnic origin had a significant risk increase (aRR 1.31) compared with women from the Nordic countries.

Sensitivity analyses comprising primiparous women only (Supporting Information Table S1) yielded almost the same associations as those shown in Table 3, including all women. The only notifiable major difference was that among primiparous women, no association was detected between maternal age of 40 years or older and OASIS risk. However, primiparous women aged 30–34 or 35–39 years were found to be at increased risk of OASIS compared with women aged 24–29 years at delivery.

Vaginal birth after previous cesarean section (VBAC) as a risk factor of OASIS was explored separately in another sensitivity analysis. The risk of OASIS among secundiparous women with one previous cesarean section (CS) (2755/29 927) was compared with that of primiparous women (25 576/429 727). We found a profound risk increase (cRR 1.60, 95% CI 1.54–1.66) of OASIS after previous CS. After adjustment for maternal characteristics the risk of OASIS remained significantly elevated (aRR 1.41, 95% CI 1.36–1.47). This risk increase could partly be explained by an increase in instrumental delivery among women undergoing VBAC, but after adjustment for delivery mode and birthweight the risk remained raised (aRR 1.24, 95% CI 1.20–1.29).

4 | DISCUSSION

Our results support the increased risk of OASIS related to well-established risk factors, including primiparity, instrumental delivery, and high birthweight.^{4,5,10} We showed a positive association with increasing maternal age, obesity (if unadjusted for birthweight), lower maternal height, and previous CS. Smoking and low maternal education level were negatively associated with OASIS.

Increasing BMI showed a decreased risk of OASIS in the crude analysis; however, it was only apparent in the adjusted model after adding birthweight to the analysis. A decreased risk of OASIS associated with increased BMI has been shown in several previous studies.^{6,16–18} However, all previously mentioned studies either adjusted for birthweight or excluded cases with babies heavier than 4000 g at birth in order to find this positive association. When interpreting our results, one must consider that obese women are at higher risk of giving birth to larger babies. The clinical relevance of an apparent protective effect associated with a higher BMI when birthweight has been adjusted for, as in previous studies, could be questioned. On the contrary, other studies have not been able to statistically detect any protective effect.^{19,20}

The proposed underlying mechanisms of a protective effect include an increased amount of adipose tissue making the perineal tissue softer and more stretchable, and a larger perineal body increasing the anovaginal distance. Another consideration is potentially increased missed diagnoses relating to difficulties in examining women with voluminous amounts of adipose tissue.⁶ In contrast, perineal tissue has

TABLE 1 Maternal characteristics and delivery mode in relation to the risk of OASIS

Characteristics		OASIS		Vaginal births		
		n	(%)	n	cRR	(95% CI)
Year of delivery	2005–2008	12226	(3.6)	335 805	1.0	Reference
	2009–2012	12370	(3.5)	357 174	0.95	0.93–0.98
	2013–2016	9987	(3.4)	296 009	0.93	0.90–0.95
Maternal age (years)	<20	349	(2.3)	15 423	0.59	0.53–0.66
	20–24	3959	(3.0)	133 787	0.77	0.74–0.80
	24–29	11 522	(3.8)	300 127	1.0	Reference
	30–34	13 037	(3.8)	341 750	0.99	0.97–1.02
	34–39	4919	(3.0)	165 330	0.78	0.75–0.80
	≥40	797	(2.4)	32 571	0.64	0.59–0.68
Parity	1	25 576	(6.0)	429 727	2.81	2.74–2.88
	2	7871	(2.1)	371 933	1.0	Reference
	≥3	1136	(0.6)	187 338	0.29	0.27–0.31
Smoking	Yes	1077	(1.8)	60 340	0.49	0.47–0.52
	No	31 891	(3.6)	882 298	1.0	Reference
	Not known	1615	(3.5)	46 360	0.96	0.92–1.01
Body mass index (kg/m ²)	<18.5	951	(4.0)	23 543	1.12	1.05–1.19
	20–24.9	20 428	(3.6)	563 735	1.0	Reference
	25–29.9	7563	(3.4)	222 729	0.94	0.91–0.96
	≥30	3022	(2.9)	103 740	0.80	0.77–0.84
	Not known	2600	(3.5)	74 627	0.96	0.92–1.00
Maternal height (cm)	<155	1159	(4.2)	27 892	1.21	1.14–1.28
	155–164	11 704	(3.6)	325 729	1.05	1.02–1.07
	165–174	16 745	(3.4)	488 258	1.0	Reference
	≥175 cm	3332	(3.3)	99 815	0.97	0.94–1.01
	Not known	1643	(3.5)	47 298	1.01	0.96–1.07
Maternal educational level	≤Primary/lower secondary	1972	(2.3)	86 794	0.55	0.52–0.57
	Upper secondary	9675	(2.9)	333 887	0.70	0.68–0.72
	<3 years higher education	4280	(3.6)	119 622	0.86	0.83–0.89
	≥3 years higher education	15 999	(4.2)	385 437	1.00	Reference
	Not known	2657	(4.2)	63 258	1.01	0.97–1.05
Maternal country of birth	Nordic countries	30 112	(3.5)	860 890	1.00	Reference
	Europe/ USA/ Canada/ Australia/ NZ	698	(3.4)	20 409	0.98	0.97–1.04
	Other	3773	(3.5)	107 699	1.00	0.97–1.05
Delivery mode	Non-instrumental	23 946	(2.6)	905 290	1.00	Reference
	Vacuum extraction	10 314	(12.6)	81 932	4.76	4.66–4.87
	Forceps	323	(18.2)	1776	6.88	6.23–7.59

Abbreviations: cRR, crude risk ratio; NZ, New Zealand; OASIS, obstetric anal sphincter injury.

been suggested to be weaker in obese women; higher BMI has been associated with striae gravidarum,²¹ which in turn have been linked to a higher risk of perineal trauma.²² It is also possible that CS is an unknown confounder; obese women are at higher risk of CS,²⁰ so those undergoing vaginal delivery might be a selected group.

Women with fewer than 9 years of education had a 15% lower risk of reported OASIS compared with those with more than 3 years of

higher education after adjusting for maternal characteristics. Similar results are seen in a Finnish study where higher socioeconomic status was associated with an 18% increased risk of OASIS.²³ A British study showed that women of high socioeconomic status were more than twice as likely to experience OASIS compared with those of low socioeconomic status.²⁴ This difference is somewhat surprising and difficult to explain. It either represents an unknown confounding

TABLE 2 Birthweight in relation to risk of OASIS

Birthweight (g)	OASIS		Vaginal births	Crude		Adjusted (maternal characteristics)		Adjusted (delivery mode)	
	N	(%)	N	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
<2500	231	(0.9)	25472	0.24	0.21–0.27	0.17	0.15–0.20	0.19	0.17–0.22
2500–2999	1845	(1.8)	101202	0.48	0.45–0.50	0.36	0.34–0.38	0.38	0.36–0.40
3000–3499	8641	(2.7)	323256	0.70	0.68–0.72	0.59	0.57–0.60	0.61	0.60–0.63
3500–3999	13713	(3.8)	357012	1.00	ref	1.00	Ref	1.00	Ref
4000–4499	7829	(5.2)	149762	1.36	1.33–1.40	1.65	1.60–1.69	1.56	1.52–1.60
≥4500	2324	(7.2)	32284	1.87	1.80–1.96	2.84	2.73–2.96	2.61	2.50–2.72

factor not accounted for, or potentially a difference in the provision of health care. The higher risk in women with higher educational level could instead represent a lower risk of missed diagnosis.

We found smoking to be negatively associated with OASIS (cRR 0.49), remaining after adjusting for maternal characteristics, and surprisingly also after adjusting for delivery mode and birthweight (aRR of 0.74). Similar results are seen in two previous Nordic studies.^{25,26} The underlying mechanisms of the apparent protective effect are unexplained. The results appear paradoxical to other known effects of smoking such as premature skin aging, reduced blood flow, and oxidative damage.²⁷ This causes us to speculate around the true protective effect of smoking, or whether a difference in provision of health care can explain the results.

Young maternal age was negatively related to risk of OASIS where women younger than 20 years of age had a 50% lower risk of OASIS compared with women aged 24–29 years. Women older than 35 years on the other hand, had an approximately 20% risk increase. The highest age group (>40 years) had a slightly lower risk increase after adjustments than women aged 34–39 years, but the difference between the risk estimates was far from significant ($p = 0.20$). Gurol-Urganci et al., showed a similar risk decrease in teenage mothers, but only a slight risk increase (aOR 1.07) in women aged 30–34 years.¹⁰ A previous Swedish study showed that the risk of OASIS increased almost continuously with age irrespective of parity, with exception for nulliparous women where the risk did not further increase after 35 years, which was similar to our findings. In this previous study, the aOR was around 2 for nulliparous women older than 30 years; however, the reference group differed from ours (<25 years), which could explain the difference in calculated risks.²⁶ Similarly, Hornemann et al. found a higher maternal age in women with OASIS compared with women with less severe perineal lacerations.²⁸ The specific effects of aging on perineal tissue have been poorly researched and the age-specific advantages of protective measures have not been studied. Considering the trends in modern society to start a family at an older age the risk should be acknowledged, and attention should be given to the importance of accurate diagnosis and treatment.

Short maternal height was positively associated with risk of OASIS. Women shorter than 155 cm had an aRR of 1.34 after adjusting for maternal characteristics. We stipulated that adjustments for delivery mode and birthweight would lessen this association, but the

correlation instead became more profound and aRR increased to 1.72, suggesting maternal height as a significant independent risk factor. Räisänen et al. found that an increase of 1 cm in maternal height decreased the risk of sphincter injury by 2%.²⁹ However, there is limited research on the effects of maternal height on obstetrical outcomes.

Our results show an increased risk of OASIS among women achieving VBAC compared with primiparous women. D'Souza et al. found a similar risk of OASIS after VBAC compared with that of primiparous women, and a 6.8-fold risk increase in secundiparous women compared with multiparous women with previous vaginal births only.³⁰ Räisänen et al. found a 1.4-fold risk increase associated with VBAC and propose an underlying fetopelvic disproportion as a potential explanation, putting women at risk of initial CS and subsequently of OASIS in following vaginal deliveries.²⁹ There might also be other confounders associated with both CS and OASIS, such as communication problems that are difficult to adjust for.

Strengths of this study include using a population-based register providing a large study population available for inclusion. This enabled analysis of multiple risk factors to produce reliable results. The Swedish Medical Birth Registry is of high quality with less than 2% missing data and is mandatory across the population providing non-selective standardized data. Nevertheless, the register contains some errors and missing values. However, the analyses did not yield any strong associations between any of the “not known” classes and risk of OASIS, suggesting that the missing information was at random—at least in relation to OASIS risk. We also recognize that the classification and diagnosis of OASIS is subjective and depends on the care provider and local routine. Furthermore, our analysis did not include fetal head circumference, length of second stage of labor, or use of anesthetic, which might impact the overall risk. We were unable to include episiotomy rates, but the national rate for primiparas in 2016 was 10%. This would have added further information, although the role of episiotomy remains to be established.⁸

5 | CONCLUSION

In this large register-based study we observed an increased risk of OASIS associated with primiparity, instrumental delivery, increasing maternal age, VBAC, and low maternal height. Obesity was observed

TABLE 3 Maternal risk factors for OASIS after multivariable modified Poisson regression analyses

		Adjusted MC		Adjusted MC + DM		Adjusted MC + DM + BW	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Year of delivery	2005–2008	1.00	Reference	1.00	Reference	1.00	Reference
	2009–2012	0.94	0.92–0.97	0.96	0.94–0.98	0.96	0.93–0.98
	2013–2016	0.92	0.90–0.95	0.97	0.94–0.99	0.96	0.94–0.99
Maternal age (years)	<20	0.45	0.40–0.50	0.50	0.45–0.56	0.49	0.44–0.55
	20–24	0.67	0.65–0.70	0.72	0.69–0.74	0.70	0.68–0.73
	24–29	1.00	Reference	1.00	Reference	1.00	Reference
	30–34	1.24	1.21–1.27	1.18	1.15–1.21	1.20	1.17–1.23
	34–39	1.29	1.25–1.34	1.18	1.14–1.22	1.23	1.19–1.27
	≥40	1.23	1.15–1.32	1.09	1.01–1.17	1.18	1.10–1.26
Parity	1	3.13	3.05–3.21	2.47	2.40–2.53	2.96	2.88–3.04
	2	1.00	Reference	1.00	Reference	1.00	Reference
	≥3	0.27	0.25–0.29	0.29	0.27–0.31	0.27	0.26–0.29
Smoking	Yes	0.64	0.60–0.68	0.65	0.61–0.69	0.74	0.70–0.79
	No	1.00	Reference	1.00	Reference	1.00	Reference
	Not known	0.95	0.88–1.03	0.96	0.88–1.04	0.96	0.89–1.04
Body mass index (kg/m ²)	<18.5	1.12	1.05–1.20	1.11	1.04–1.18	1.30	1.22–1.38
	20–24.9	1.00	Reference	1.00	Reference	1.00	Reference
	25–29.9	1.07	1.04–1.10	1.06	1.04–1.09	0.97	0.94–0.99
	≥30	1.04	1.04–1.10	1.04	1.00–1.08	0.90	0.87–0.94
	Not known	1.01	0.95–1.08	1.02	0.95–1.08	0.98	0.92–1.04
Maternal height (cm)	<155	1.34	1.26–1.42	1.24	1.17–1.31	1.72	1.62–1.82
	155–164	1.11	1.08–1.13	1.07	1.04–1.09	1.23	1.21–1.26
	165–174	1.00	Reference	1.00	Reference	1.00	Reference
	≥175	0.92	0.88–0.95	0.94	0.91–0.98	0.82	0.79–0.85
	Not known	1.03	0.93–1.14	1.01	0.92–1.12	1.09	0.99–1.21
Maternal education level	≤Primary/lower secondary	0.85	0.81–0.89	0.84	0.80–0.88	0.87	0.83–0.92
	Upper secondary	0.88	0.85–0.90	0.87	0.85–0.89	0.87	0.85–0.90
	<3 year higher education	0.92	0.89–0.95	0.92	0.89–0.95	0.92	0.90–0.96
	≥3 year higher education	1.00	Reference	1.00	Reference	1.00	Reference
	Not known	0.94	0.90–0.98	0.93	0.89–0.97	0.95	0.91–0.98
Maternal country of birth	Nordic countries	1.00	Reference	1.00	Reference	1.00	Reference
	Europe/ USA/ Canada/ Australia/ NZ	0.91	0.84–0.98	0.91	0.84–0.98	0.92	0.86–0.99
	Other	1.21	1.17–1.25	1.20	1.16–1.24	1.31	1.26–1.35
Delivery mode	Non-instrumental					1.00	Reference
	VE					2.79	2.73–2.86
	Forceps					4.27	3.86–4.72

Abbreviations: BW, birthweight; DM, delivery mode; MC, maternal characteristics; NZ, New Zealand; OASIS, obstetric anal sphincter injury; RR, risk ratio.

to slightly increase the risk of OASIS if adjustments for birthweight were not made but the mechanisms of this association remain unclear. A negative association with OASIS was seen with smoking and low maternal educational levels; however, there are uncertainties

whether this association represents a true protective effect or a potential difference in the provision of health care. Future studies will be able to use these results in a clinical setting aimed at individual risk assessment improving women's health.

AUTHOR CONTRIBUTIONS

KA, AS, and KK contributed to the overall design of the study and the analysis and interpretation of the data. KA drafted the first manuscript. AS and KK then revised and critically appraised the draft before all authors approved of the final manuscript.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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