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Stable incidence but regional differences in retinopathy of prematurity in Norway from 2009 to 2017

Beanca Gjølberg Grottenberg,[1,2]* Katinka Madtzog Korseth,[1,3] Turid Follestad,[4] Hans Jørgen Stensvold,[5,6] Ragnhild Støen[1,7†] and Dordi Austeng[8,9†]

[1]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[2]Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway
[3]Department of Neurology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[4]Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway
[5]Norwegian Neonatal Network, Oslo University Hospital, Oslo, Norway
[6]Neonatal Department, Division of Paediatric and Adolescent Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway
[7]Department of Neonatology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[8]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
[9]Department of Ophthalmology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

ABSTRACT.

Purpose: **To explore the changes over time and regional differences in the incidence of retinopathy of prematurity (ROP) in a national cohort of infants born <28 weeks' gestational age (GA).**

Methods: **A population-based study of infants with GA <28 weeks in Norway from 2009 to 2017. Prospectively collected data on clinical variables and outcomes were obtained from the Norwegian Neonatal Network.**

Results: **Of 1499 live-born infants transferred to a neonatal intensive care unit, 1156 were discharged alive. Four-hundred and fifty-eight infants (39.6%) had ROP, 152 (13.1%) had severe ROP, and 110 (9.5%) were treated for ROP. Eleven hundred infants (95.2%) had complete data sets. In a model comprising region of primary care, GA [odds ratios (OR): 0.65; 95% CI: 0.55–0.77], growth velocity (OR: 1.10; 95% CI: 1.00–2.00), medically treated patent ductus arteriosus (OR: 1.80; 95% CI: 1.19–2.72), weeks of supplemental oxygen (OR: 1.07; 95% CI: 1.03 to 1.11) and region of primary care (OR: 4.95; 95% CI: 3.05–8.04 for the pair of regions with the highest estimated OR) were significantly associated with severe ROP. Additionally, institutional differences for severe ROP were found, with ORs from 0.41 (95% CI: 0.05–3.23) to 5.36 (95% CI: 3.05–9.43) using the largest institution as reference. Incidences were stable over time after adjusting for GA. A larger proportion was treated with anti-vascular endothelial growth factor after 2011.**

Conclusions: **The incidence of severe ROP was stable between 2009 and 2017 in Norway. Regional and institutional differences need to be explored in future studies.**

Key words: anti-VEGF – incidence – population-based study – regional differences – retinopathy of prematurity – risk factors

*Shared co-first authorship.

†Shared last authorship.

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Introduction

Retinopathy of prematurity (ROP) has become one of the most important causes of avoidable childhood blindness (Hellstrom et al. 2013; Shah et al. 2016) and is caused by abnormal growth of retinal blood vessels that may result in retinal scarring and detachment. Lower gestational age (GA) and lower birthweight (BW), in addition to oxygen exposure, are well-

known risk factors for ROP (Hellstrom et al. 2013; Darlow et al. 2005a; Darlow et al. 2005b), but the aetiology is multifactorial (Hellstrom et al. 2013) and the disease persists in spite of changes in neonatal care over the last decades (Austeng et al. 2009).

An association between increased incidence of ROP and increased oxygen saturation (SpO_2) targets has been suggested in Sweden (Holmstrom et al. 2018) and Australia (Manley et al. 2016). Norway has no national consensus on oxygen saturation target policies for preterm infants, and previous studies have shown no change in the incidence of ROP since the late 90s until 2014 (Markestad et al. 2005; Stensvold et al. 2017). However, European guidelines have changed after 2013 (Sweet et al. 2013), and Norwegian neonatal intensive care units (NICUs) may have changed their saturation targets accordingly.

Regional and institutional differences in ROP have been discovered in Sweden (Austeng et al. 2014; Holmstrom et al. 2018), Canada (Thomas et al. 2015) and Australia (Darlow et al. 2005a; Darlow et al. 2005b). Such differences have been linked to variation in neonatal care, especially different oxygen targets and routines of monitoring oxygen levels and delivery (Darlow et al. 2005a; Darlow et al. 2005b; Holmstrom et al. 2018). Whether such variations exist in Norway is not known. Since each of the four Norwegian health regions has chosen different organizational structures for neonatal care, regional and institutional differences are of interest.

The aim of the present study was to evaluate incidences of ROP, clinical risk factors and potential regional and institutional differences in a 9-year national Norwegian cohort. In addition, changes in treatment strategies for ROP over time were explored.

Materials and Methods

This population-based registry study includes 1156 infants discharged alive born from 22^0 to 27^6 gestational weeks between 1 January 2009 and 31 December 2017. Complete data were available for 1100 (95.2 %) of these infants. Location of primary care was classified according to hospital of birth or, if transferred during the first 24 hr of life, to the hospital the infant was transferred to. The organizational structure of neonatal care in Norway varies between the four health regions, with two to four NICUs per region providing care to infants born before GA 28 weeks and one or two NICUs per region providing care to infants born before GA 26 weeks.

Data collection

Data were collected from the Norwegian Neonatal Network (NNN), a governmental-funded national medical quality registry for infants admitted to a neonatal unit. The NNN was established as a national medical quality registry in 2004. The registry reached a complete nationwide coverage on regionalized preterm infants in 2008, and on all infants admitted to a NICU in 2012. The NNN includes data on delivery, treatments, invasive procedures, diagnosis and short-term outcomes before discharge from the NICU. Norwegian Neonatal Network (NNN) collects personal identifiable data without consent according to the Medical Birth Registry Regulation and the Personal Health Data Filing Systems Act of Norway.

Ethics

Ethical approval for this study was obtained from the Regional Committees for Medical and Health Research Ethics (REK) in Norway (ref. 2016/1894). The study was conducted following the principles of the Declaration of Helsinki.

Outcomes and variable definitions

Retinopathy of prematurity (ROP) was classified according to the International Classification of ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005). During the years 2009–2017, the NNN holds data on the highest stage of ROP in either eye as identified on examinations with indirect ophthalmoscopy. Whether the child is treated for ROP and the method of treatment are also recorded. According to the national guidelines, infants born before GA 32 weeks are examined regularly for ROP with intervals of 2 weeks or less (Austeng & Lindqvist 2017). Those born before 28 weeks have their first eye examination at PMA 31 weeks. Severe ROP was defined as stage 3 or higher. The use of laser and/or intravitreal anti-VEGF (vascular endothelial growth factor) therapy defined the treated ROP group. Criteria for treatment followed the recommendations of the Early Treatment of ROP (ETROP) study (Early Treatment for Retinopathy of Prematurity Cooperation Group 2003). From 2011, the national guidelines include recommendations of using anti-VEGF treatment in children with zone I ROP (Mintz-Hittner et al. 2011).

Necrotizing enterocolitis (NEC) was defined as Bell's stage 2 or 3 (Bell 1978). Severe intraventricular haemorrhage (IVH) was diagnosed on cerebral ultrasound according to Papile grades 3–4 (Papile et al. 1978).

All pregnant women in Norway are entitled to antenatal care free of charge. Gestational age (GA) is calculated based on ultrasound dating at routine fetal ultrasound between 17 and 19 weeks' gestation. If no fetal ultrasound before 20 weeks' gestation is available, calculation is based on last menstrual period (Stensvold et al. 2017). Small for GA (SGA) was defined as BW below the 10th centile according to the Norwegian growth charts (Skjaerven et al. 2000).

Growth velocity (GV; grams per kilogram per day) was calculated based on an exponential model using weights at birth and PMA 36 weeks (Patel et al. 2005).

Statistical analysis

All statistical analyses were performed with SPSS 25.0 (SPSS Inc., Armonk, NY, USA). The data are presented as mean with standard deviation (SD) and median with 25th and 75th percentiles or numbers with proportion (%). Logistic regression modelling was applied to investigate clinical risk factors for severe ROP. The results from the logistic regression analyses are presented as odds ratios (OR) with 95% CI: and p-values. p-values <0.05 were considered statistically significant.

Changes in the incidence of severe and treated ROP during the study period were analysed using a logistic regression model with year, treated as a categorical variable, and GA, treated as a continuous variable, as explanatory variables.

The selection of the 10 predetermined variables included in the multivariate model, in addition to regions,

Table 1. Demographic variables and neonatal morbidity among 1156 infants born before 28 weeks of gestation in Norway between 2009 and 2017, systematized as with or without severe ROP (ROP stage 3 or more).

	Severe ROP	
	Yes *N* = 152	No *N* = 1004
GA (weeks), mean (SD)	25.3 (1.3)	26.3 (1.2)
BW (g), mean (SD)	685.7 (158.0)	852.4 (199.6)
Female, *n* (%)	72 (47.4)	474 (47.2)
ANS (*N* = 1150), *n* (%)	141 (92.8)	901 (90.3)
SGA, *n* (%)	39 (25.7)	197 (19.6)
Any vasopressor treatment, *n* (%)	57 (37.5)	172 (17.1)
PDA medical treatment, *n* (%)	87 (57.2)	306 (30.5)
PDA surgical treatment, *n* (%)	15 (9.9)	63 (6.3)
NEC Bell's stage 2–3 (*N* = 1153), *n* (%)	20 (13.2)	35 (3.5)
IVH grade 3–4, *n* (%)	16 (10.5)	59 (5.9)
BPD, *n* (%)	123 (80.9)	496 (49.4)

Categorical variables are expressed as *n* (%) and continuous variables as mean with SD. For variables with missing data, the number of observed values (*N*) is indicated.
ANS = antenatal steroids, BPD = bronchopulmonary dysplasia, BW = birthweight, GA = gestational age, IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, ROP = retinopathy of prematurity, SGA = small for gestational age.

was based on previous tentative risk factors for ROP (Kim et al. 2018). In cases of strongly correlated covariates that were related to the same morbidity (e.g. mechanical ventilation and oxygen therapy), only one was chosen. Any use of vasopressor was included as a marker of early haemodynamic instability and duration of supplemental oxygen as a marker of severity of lung disease. Gestational age (GA), SGA, exposure to antenatal steroids, postnatal GV, medically treated patent ductus arteriosus (PDA), NEC, IVH grades 3–4 and duration of parenteral nutrition (PN), including lipids, were also included in the model.

Assessing regional differences, the four regions of primary care were included in the model as a categorical variable. The region with the largest patient population was set as reference for the analysis. Differences between the 10 institutions with >10 patients included were also analysed using the largest unit as a reference.

Results

Of 1499 live-born infants admitted to a NICU, 1156 (77.1%) were discharged alive and comprised the study population. Mortality before discharge was 34.2% and 13.5% among infants with GA <26 weeks and GA 26–27 weeks, respectively.

Of the 1156 infants, 458 (39.6%) had any ROP, 152 (13.1%) had severe ROP, and 110 (9.5%) were treated for ROP. Mean GA was 26.2 weeks (SD 1.3) and median GA 26.6 weeks (25th and 75th percentiles: 25.1 and 27.1). Mean BW was 830 grams (SD 203) and median 828 grams (25th and 75th percentiles: 680 and 980). Two hundred and thirty-six infants (20.4%) were SGA, and 546 (47.2%) were females. Background variables for infants with and without severe ROP are shown in Table 1.

The incidence of severe ROP was inversely associated with GA (Fig. 1A). The incidence per year is shown in Fig. 1B. Using 2009 as the reference and adjusting for GA, there was no evidence of an increase in OR for neither severe nor treated ROP during the study period (p = 0.910 and p = 0.363 for severe and treated ROP, respectively).

Table 2 shows the association between regions and severe ROP adjusted for GA. Associations between

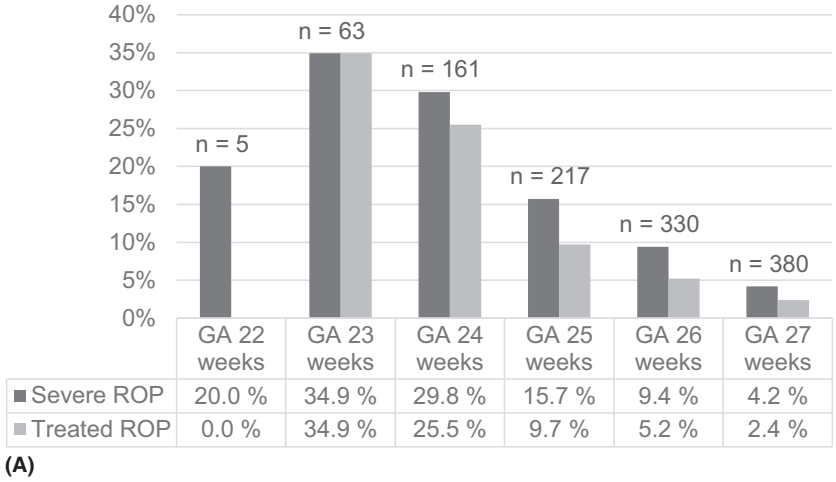

Fig. 1. (A) The incidence of severe ROP (ROP stage 3 or more) and treated ROP per gestational week. The total number of infants in each gestational age group is shown with *n*. (B) The incidence of severe ROP (ROP stage 3 or more) and treated ROP per year, unadjusted for gestational age. The total number of infants in each gestational age group is shown with *n*. ROP = retinopathy of prematurity.

the 10 predetermined clinical variables and severe ROP, with and without geographical region as a variable, are shown in Table 3a,b, respectively. Lower GA, lower GV, medically treated PDA, weeks of supplemental oxygen and region of primary care demonstrated significant associations with severe ROP in the model (Table 3b).

The estimated odds of severe ROP was 5.36 (95% CI: 3.05 to 9.43) times higher among infants in the institution with the highest odds, and 2.44 times lower (OR: 0.41, 95% CI: 0.05 to 3.23) in the institution with the lowest odds, compared with the reference hospital after adjusting for GA (Fig. 2). Similar results were found for treated ROP (results not shown).

Considering only the 152 infants with severe ROP, 99 (65.1%) received treatment in this group. Sixty-three (63.7%) of these had only laser therapy, 22 (22.2%) were treated with intravitreal anti-VEGF therapy only, and 14 (14.1 %) were treated with both laser and anti-VEGF. Among infants born at GA 23–24 weeks, 21 (33.3%) of 63 infants were given intravitreal anti-VEGF therapy as the only treatment, while this was the case for 6 (15.8%) of the 38 infants with GA 25–26 weeks. Frequency of treatment and treatment modalities according to GA and year are shown in Fig. 3A,B, respectively.

Table 2. Estimated odds ratio (OR) for severe ROP (ROP stage 3 or more) in each of the four regions.

		95% CI for OR		
With regions adjusted for GA	OR	Lower	Upper	p-value
GA, weeks	0.50	0.43	0.57	<.001
Regions (reference: Region 1)				
Region 2	4.16	2.69	6.42	<.001
Region 3	2.29	1.32	3.98	0.003
Region 4	1.75	0.87	3.52	0.115

Results from logistic regression analyses.
ROP = retinopathy of prematurity.

Table 3. Factors associated with severe ROP (ROP stage 3 or more) in 1100 infants with GA <28 weeks.

		95% CI for OR		
a) Without regions	OR	Lower	Upper	p-value
GA, weeks	0.69	0.58	0.81	<.001
ANS	1.27	0.61	2.64	0.518
SGA	1.22	0.74	2.00	0.436
GV	1.03	0.95	1.12	0.429
PDA medical treatment	1.64	1.10	2.44	0.014
NEC Bell's stage 2–3	1.82	0.76	4.35	0.178
IVH grade 3–4	1.47	0.77	2.79	0.241
Duration of supplemental oxygen, weeks	1.06	1.02	1.10	0.001
Any vasopressor treatment	1.60	1.03	2.48	0.037
Duration of PN, days	1.00	0.99	1.01	0.476

		95% CI for OR		
b) With regions	OR	Lower	Upper	p-value
GA, weeks	0.65	0.55	0.77	<.001
ANS	1.08	0.52	2.27	0.833
SGA	1.10	0.66	1.84	0.708
GV	1.10	1.00	2.00	0.040
PDA medical treatment	1.80	1.19	2.72	0.005
NEC Bell's stage 2–3	2.39	0.94	6.09	0.069
IVH grade 3–4	1.64	0.83	3.23	0.151
Duration of supplemental oxygen, weeks	1.07	1.03	1.11	0.001
Any vasopressor treatment	1.16	0.73	1.86	0.533
Duration of PN, days	1.01	1.00	1.02	0.217
Regions (reference: Region 1)				
Region 2	4.95	3.05	8.04	<.001
Region 3	2.26	1.23	4.15	0.009
Region 4	1.27	0.60	2.71	0.532

Results from logistic regression analyses, both without and with regions.
ANS = antenatal steroids, GA = gestational age, GV = growth velocity, IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, PN = parenteral nutrition including lipids, ROP = retinopathy of prematurity, SGA = small for gestational age.

Discussion

The incidence of ROP among extremely preterm infants was stable over a 9-year period from 2009 to 2017 in Norway. Gestational age (GA) was the risk factor with the strongest evidence of an association with severe ROP. Regional, as well as institutional, differences persisted after adjusting for well-known clinical risk factors.

The present study found a lower incidence of severe ROP compared with the Extremely Preterm Infant Study in Sweden (EXPRESS) (Austeng et al. 2009) (17.5% versus 34.8% among infants less than GA 27 weeks in the present and the EXPRESS study, respectively), but similar incidence as in an Austrian study of infants born in 1999–2001 (Weber et al. 2005). The higher incidence found in the EXPRESS study could at least partly be explained by a large proportion of infants born before 24 weeks GA (11% versus 5.9%, EXPRESS and present study, respectively) (Austeng et al. 2009). With 35% reduced odds of severe ROP for each additional gestational week, as found in the present study, the incidence may be affected by only small changes in the proportion of the most immature infants (Darlow et al. 2005a; Darlow et al. 2005b; Austeng et al. 2009). After adjusting for GA, there was no evidence of an increase in neither severe nor treated ROP from 2009 to 2017, but the frequency of treated ROP was almost doubled from the first Norwegian

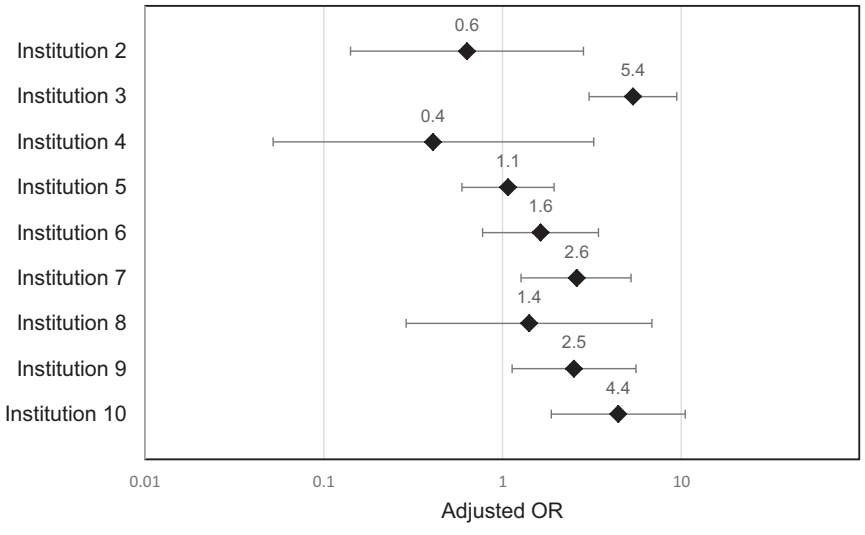

Fig. 2. Estimated odds ratio (OR) for severe ROP (ROP stage 3 or more) in 1135 infants from the 10 institutions with >10 infants included, adjusted for gestational age in a logistic regression model. Institution number 1 (with the highest number of included infants) is used as reference. Observe that a logarithmic scale is used for the *x*-axis. ROP = retinopathy of prematurity.

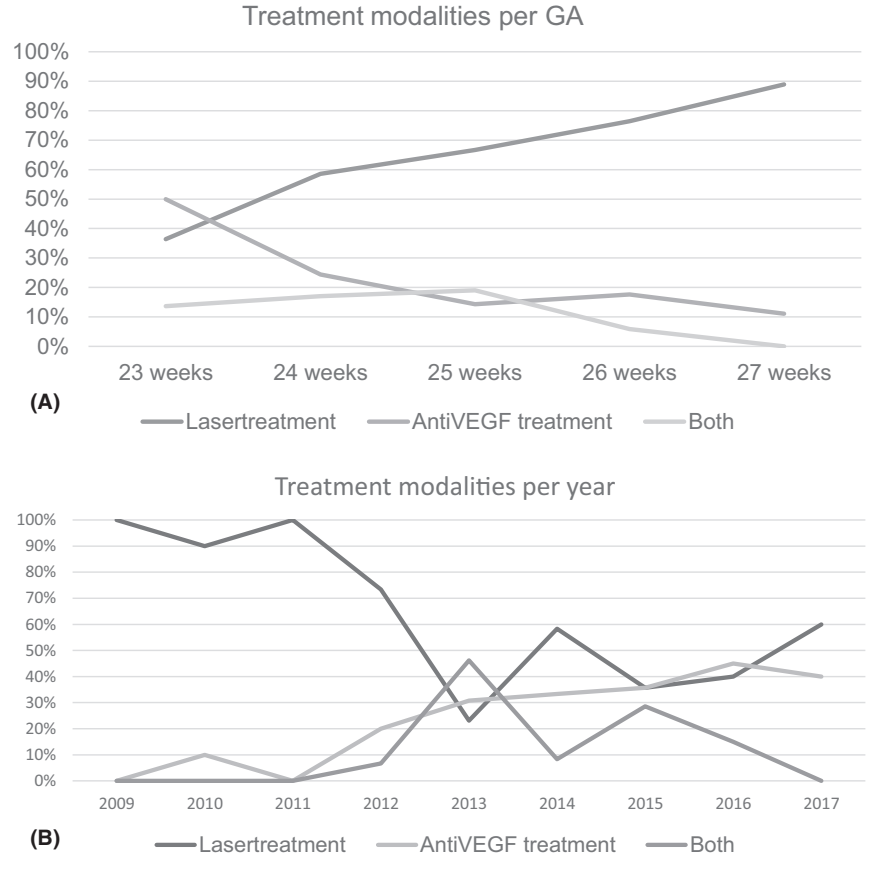

Fig. 3. (A) Treatment modalities according to gestational age. No infant born before 23 weeks was treated for retinopathy of prematurity (ROP). (B) Treatment modalities according to year.

Extreme Prematurity Study (NEPS1; infants born in 1999–2000) (Markestad et al. 2005). A similar increase in the frequency of treated ROP was seen in infants born at 22–26 weeks' gestation from 1995 to 2006 in the United Kingdom and Ireland (Costeloe et al. 2012) and may, at least partly, be attributed to better quality of retinal screening and lower thresholds for treatment (Early Treatment for Retinopathy of Prematurity Cooperation Group 2003).

The odds for severe ROP increased with approximately 7% for each additional week of supplemental oxygen in our multivariate model. We have no data in the present study to support or refute an effect of any practice change caused by the new European guidelines from 2013, aiming for oxygen saturation between 90% and 94% (Sweet et al. 2013). In Sweden, an association between increased incidence of ROP and increased oxygen saturation targets has been suggested (Holmstrom et al. 2018). In Canada, however, a decrease in severe ROP over the last decade has been attributed to the implementation of oxygen saturation targeting policies (Thomas et al. 2015). A national oxygen saturation policy may increase awareness and staff vigilance to comply with the guidelines, and implementation of a training programme for nurses has been shown to increase time within oxygen saturation targets and decrease both hyperoxia and hypoxia (van Zanten et al. 2017).

There was some evidence of an association between GV and severe ROP in the present study. This is similar to the Swedish EXPRESS study (EXPRESS Group, 2010), as well as the e-ROP study (Ying et al. 2015). The association between low postnatal weight gain and ROP has been explained by low insulin-like growth factor 1 levels and lower retinal vessel growth in infants with slow postnatal growth (Hellstrom et al. 2003). Recent studies suggest that the association between weight gain and ROP is more complex than previously thought (Bal et al. 2019). It may be that both ROP and slow postnatal growth are seen in the youngest infants who have more prematurity-related comorbidities in general. Such comorbidities (e.g. NEC, chronic lung disease, PDA) also have in common that they are linked to systemic inflammation during the first postnatal month (Martin et al. 2013; O'Shea et al. 2013; Holm et al. 2017). Unfortunately, this study did not have access to data on sepsis or other markers of systemic inflammation.

In accordance with our findings, the presence of a clinically significant PDA has been reported by many to be associated with ROP (Kumar et al. 2011; Thomas et al. 2015; Gebesce

et al. 2016). This study, which was based on registry data, could only collect data on PDA related to treatment. A change in retinal perfusion caused by nonsteroidal anti-inflammatory drugs such as indomethacin (Abran et al. 1995) may lead to increased ocular production of VEGF and increased retinal neovascularization, and has been used to explain an association between medically treated PDA and ROP (Jegatheesan et al. 2008; Tsui et al. 2013). However, the results are conflicting, and Goldman et al. reported that indomethacin may have a protective role in the development of severe ROP in very low-BW infants (Goldman et al. 2010).

Retinal laser treatment was the standard treatment method in 2009. During the study period, intravitreal injections with anti-VEGF emerged as an efficient therapeutic alternative especially for the youngest infants (Mintz-Hittner et al. 2011). The observed increase in anti-VEGF treatment is in line with recently published treatment trends from some countries (Walz et al. 2018), but stronger than reported by others (Adams et al. 2017; Holmstrom et al. 2020). We did, unfortunately, not have data on whether all children treated with anti-VEGF had zone I disease or not during the study period, but such data are included in the NNN from 2017.

There was an up to fivefold difference in odds of severe ROP between health regions in the present study, after adjusting for relevant perinatal risk factors. This finding is in accordance with other studies demonstrating regional and institutional differences in severe and/or treated ROP (Darlow et al. 2005a; Darlow et al. 2005b; Austeng et al. 2014; Thomas et al. 2015; Holmstrom et al. 2018). Our study cannot differentiate between real differences in disease incidence and differences in interpretation of retinal findings or inter-observer variation in diagnosis. Inter-observer variation has previously been suggested to highly contribute to regional variations (Darlow et al. 2008). Disagreement between examiners concerning the presence of threshold disease was found in 12% of patients in the CRYO-ROP study (Reynolds et al. 2002) and is also demonstrated in recent studies (Slidsborg et al. 2012). The availability of retinal imaging has made it possible to share images and to provide remote assessment of retinal development to define which infant warrants referral to an institution where expert evaluation and treatment can be given (Cheng et al. 2019). More consistent use of retinal imaging and the use of central readers may clarify the role of inter-observer variation in the interpretation of retinal findings.

In conclusion, this national registry study demonstrates stable ROP incidence over the last 9 years, but a shift towards more use of intravitreal injections with anti-VEGF to treat ROP. Regional and institutional differences were found after adjusting for clinical risk factors and warrant further investigations.

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Correspondence:
Dordi Austeng
Department of Neuromedicine and Movement Science
Norwegian University of Science and Technology
Trondheim
Norway 7491
Tel: +47 47352135
Fax +47 72575765
Email: dordi.austeng@ntnu.no

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