



# Regaining birth weight and predicting ROP—a prospective, pilot study

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**Background:** Poor postnatal weight gain is a well-known risk factor for developing retinopathy of prematurity (ROP). Algorithms that predict ROP based on serial weight gain have not been generalizable in non-Caucasian populations. The duration taken to regain the lost weight is culturally important among Indian mothers. We report the correlation between this duration and the risk of developing ROP.

**Methods:** Sixty-eight Asian Indian infants born <2,000 grams at birth or <34 weeks of gestation were enrolled. The number of days taken for these infants to regain baseline birth weight (BW) was recorded. This measure was correlated with the eventual ROP outcome categorized as “no ROP”, ROP that regressed spontaneously (type 2 ROP), and ROP that required treatment (type 1).

**Results:** The mean BW of the cohort was 1,270±340 grams and mean gestational age (GA) was 31±2 weeks. Thirty-three infants (48.5%) developed no ROP, 20 infants (29.4%) developed type 2 ROP and 15 infants (22.1%) developed type 1 ROP. The mean number of days to regain the lost weight was 11.9±4.6, 17.9±7.9 and 26.6±12.9 days for the No ROP, type 2 and type 1 groups respectively ( $P<0.0001$ , one-way ANOVA with Bonferroni correction). Those babies who regained their BW within 10 days were at least risk of developing any stage ROP, moderate risk if they took between 11–20 days and highest risk if they took more than 21 days for developing type 2 or type 1 ROP.

**Conclusions:** The date when a child regains its lost BW is culturally important and easily recalled by mothers. We report the use of this simple estimate as a predictor of ROP. This method could be useful in stratifying risk and predicting the development of “treatment requiring ROP” even before 21 days of life, which is the first mandated screening visit in India.

**Keywords:** Retinopathy of prematurity (ROP); birth weight (BW)

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## Introduction

Retinopathy of prematurity (ROP) is the leading cause of preventable blindness in infants world-wide. Countries like India and other middle-income countries are believed to be suffering from the third epidemic (1,2). ROP screening is performed by using screening criteria of birth weight

(BW) and or gestational age (GA) although there are several other systemic risk factors that may contribute in different measures to the outcome of ROP in an infant (3-5).

In India, infants born < or equal to 2,000 grams and/or < or equal to 34 weeks of GA are screened before they turn 30 days old (6). However, GA assessment in a vast majority

of rural mothers is inaccurate leading to discrepancies in enrolment into the screening program. BW assessment is a more robust and accurate measurement, and is reliably available in most babies, even in non-institutional and rural deliveries (7). This has led to BW becoming the single most important criteria for enrollment into the ROP screening program.

With the national emphasis on BW, the quest to develop simple tools that may be able to predict “at-risk” babies has been a constant endeavor. One innovative, low-cost method of risk stratification is by capturing serial postnatal weight gain, which is a surrogate for insulin-like growth factor 1 (IGF-1) (8-11). Predictive models have demonstrated accurate ROP risk assessment and a reduction in the proposed number of ROP examinations. These include, WINROP, a computer-based algorithm that identifies cumulative deviations from the expected weight gain, ROPScore—a spreadsheet-based equation, and CHOP ROP, a normogram based model that uses a single equation with BW and GA and weight gain (12,13). Limitations of these models include a precise estimate of sensitivity and poor generalizability of these models to countries with higher BW and GA infants that require treatment, like in India (14). Most of these models require serial, daily weight measurements up to 6 weeks or more after birth. In the Indian scenario, where infants are discharged from the neonatal intensive care unit (NICU) early, this is not always feasible, since there is poor compliance for follow-up after discharge of the baby.

In this pilot study we attempt to correlate the day of life when the baby regains its initial loss of body weight after birth with the final outcome of ROP. We noted that mothers remembered this day with accuracy, because of a cultural belief that a child who has regained its BW has a better chance of survival. The primary outcome of the study was to evaluate the correlation between the duration (in days) required to regain BW with the development of ROP. As a secondary outcome, we used this duration to stratify risk, which has the potential to influence the follow-up schedule.

## Methods

Preterm, Asian Indian infants who were enrolled for ROP screening in the Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KIDROP) tele-ROP program, were enrolled into the study. All babies fulfilled the national screening guidelines of  $\leq 2,000$  grams and/or  $\leq 34$  weeks

of gestation. Those infants who lacked complete hospital records, or were unsure of the weight change measures or who were lost to follow-up before the final ROP status could be documented, were excluded from the study.

Sixty-eight consecutively enrolled infants who fulfilled the study criteria were included for the analysis. Chart records of weight (grams) measured daily using a digital weighing scale, were accessed while the baby was admitted in the respective NICU. In discharged cases (6/68 babies), the mother was contacted telephonically and asked to get the infant weighed at a local center and the value was noted. These weight measures were noted until the baby “regained their respective BWs” rounded off to the closest whole integer. This “age of regaining BW” value was correlated with the eventual retinal status of all enrolled babies. While we prospectively and independently collected the daily BWs of these infants from the nursing charts, the mothers were also separately asked to recall the date of regaining lost weight at the end of the study period.

The outcome was divided into no ROP, ROP which regressed spontaneously (type 2 ROP), and ROP which required treatment (type 1) as per the ICROP classification (15). Computing these values, a risk score was estimated to predict which babies would develop the disease. IBM SPSS ver23 and MedCalc were used for statistical analysis and plots. One-way ANOVA with Bonferroni correction was applied to test the mean difference between the groups (no ROP, type 2 and type 1).

The study fulfilled the requirement of the Institute Research Board (IRB) and was approved by the Institute Ethics Committee (IEC). Written, informed consent was obtained from the parents or legal guardians of all the study recruits.

## Results

Of the 68 patients enrolled in the study, 33 infants (48.5%) did not have any ROP, 20 infants (29.4%) had type 2 ROP and 15 infants (22.1%) had type 1 ROP.

The mean BW of the study cohort was  $1,270 \pm 340$  grams and the mean GA was  $31 \pm 2$  weeks. The mean difference in BW, GA and number of days to regain BW was found to be significantly different between the three groups ( $P < 0.001$ ). On applying Bonferroni correction, the mean BW was comparable between no ROP and type 2 ( $P = 0.08$ ) and between type 1 and type 2 ( $P = 1.00$ ) and was significantly different between no ROP and type 1 ( $P = 0.013$ ). The mean GA was significantly different between no ROP *vs.* type 2

and no ROP *vs.* type 1 ( $P < 0.001$ ) comparable between type 2 and type 1 ( $P = 1.00$ ).

### Days required to regain BW

All 68 mothers (100%) were able to accurately recall the date on which their infant had regained the lost weight. The mean number of days for the No ROP group to regain BW was  $11.9 \pm 4.6$  days, for the type 2 ROP group was  $17.9 \pm 7.9$  days and for the type 1 ROP group was  $26.6 \pm 12.9$  days respectively. To reduce the influence of outliers on the mean values, we performed a robust fit analysis and found they were comparable (no ROP 11.9 days, type 2 ROP 17.6 days and type 1 ROP 24.8 days respectively). The number of days to regain BW was significantly different between no ROP *vs.* type 1 and no ROP *vs.* type 2 and type 1 *vs.* type 2 ( $P < 0.001$ ).

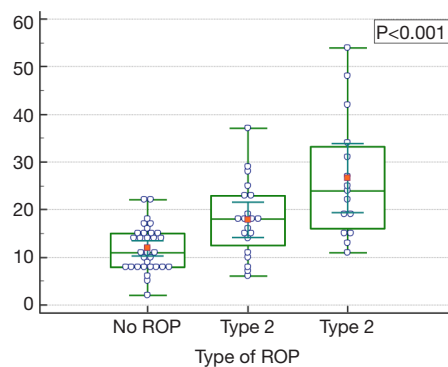
### Risk stratification

The mean and distribution of the age at regaining BW is depicted in *Figure 1*. In this study cohort, no baby developed any stage ROP if it regained its BW in 6 or less days and all babies who took 37 or more days to regain their weight developed type 1 ROP. We used the 95% confidence intervals of the groups to develop a generalizable risk stratification. Those babies who regained their BW within 10 days were at the least risk of developing any stage ROP. Those who took 11–20 days were at moderate risk and those who took more than 21 days were at the highest risk of developing type 2 or type 1 ROP.

### Discussion

ROP has become an important public health concern in middle-income countries. India and China lead the world in the number of preterm infants with the former accounting for over 3.5 million annually (16). With an overall increase in survival, improved neonatal care delivery especially in the rural hospitals, improved awareness about ROP, and more recently a spurt in medical negligence cases against institutes not providing timely and appropriate ROP screening or referral, the quest for an ideal screening program has become a policy concern for the federal and state governments in India (17).

As with any public health initiative, a program's success is measured by the enrolment of those who are "at risk". ROP screening is based on an "opportunistic



**Figure 1** Mean and distribution of the age at regaining birth weight (BW) in the three groups.

screening" model with the NICU being the focus. Measures to detect "risk factors" that can "predict" which babies eventually progress to developing ROP are constantly being researched. This leads to modifications in the screening protocol to address regional concerns. For example, despite the clinical unlikelihood of ROP being present or detected within 1 week of life, a recent study from India showed that by screening babies before discharge from the NICU (even if a few days old), the yield of enrolment, detection and follow-up were better than if the conventional "30-day-rule" was followed (18).

Cultural beliefs and social norms in neonatal care may influence ROP screening. In this study, we evaluated a culturally prevalent parameter with its outcome on ROP, i.e., the timing of regaining BW after a baby had lost its initial weight after birth. Culturally, a baby who has regained his or her weight is considered to be more likely to survive than a baby who did not. The recall value of this date was exploited in this study, especially amongst mothers. We found that all mothers accurately recalled the date on which their infants had regained this weight in our study.

Predictive models including WINROP, ROPScore and CHOP ROP are limited by their sensitivity, lack of generalizability especially in non-Caucasian populations and often require accurate daily weight recordings for over 6 weeks or more before the alarms for ROP risk can get flagged (12–14). The advantages of these tools however remain in their long track record, validated computer based algorithms and high sensitivity in the population it was originally tested in (13). Whereas it may be argued that in our study we too relied on daily weight recordings, there are two fundamental differences. Firstly, our recording stopped when the baby regained its BW which was

considerably shorter than what is required in the other tools. Secondly, since we saw that the recall of the mothers was very accurate, eliciting the daily weight record may not be necessary. However, it needs to be evaluated in a larger community setting before this conclusion is made.

The limitations of the study include its relatively small sample size of 68 infants. Besides, the number of babies developing any stage and treatment requiring ROP were higher in proportion than that is prevalent in the community. This bias is likely because we only enrolled infants who had daily weight records accurately measured which was possible mostly in those admitted for longer periods in the NICU. These were most often the sickest infants who were most likely to develop ROP. However, the babies were enrolled from over 35 NICU's across our screening network, and are less likely to have center specific admission bias. Secondly, we did not assess other comorbidities in the perinatal period. Though they have the potential to impact ROP outcome, these were deliberately left out of the study to allow assessment of regaining BW as an independent and simple tool to determine ROP risk. Finally, our cohort comprised of a homogenous Asian Indian ethnicity and needs to be validated in other ethnic groups.

The national ROP screening guidelines in India recommends that all babies  $\leq 2,000$  grams, be "first" screened before "30 days of life". The recommended first screening date is between 3–4 weeks for babies born  $>1,200$  grams and between 2–3 weeks for those born below 1,200 grams (6). Our results may help in stratifying risk before they are initiated into the screening program. If a baby regains its weight within 10 days of life, the risk of developing ROP appears to be the least. If the baby takes more than 21 days, the risk is the highest. Hence the ROP specialist and the neonatologist could use the weight regaining date as an additional risk factor while enrolling a baby into the program. Those infants at higher risk could also be advised closer follow-up. This will also act as a good tool to counsel parents especially if they are discharged within 1 month of birth.

This pilot study demonstrates a simple tool that is culturally acceptable, easily accessible and can be recorded without any additional cost to the parents or the treating hospital.

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None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study fulfilled the requirement of the Institute Research Board (IRB) and was approved by the Institute Ethics Committee (No. ECR/187/Inst/Kar/2013:C/2015/05/09) and written informed consent was obtained from all patients.

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