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Impact of maternal Iron deficiency anemia on survival of small newborns: A prospective cohort in Kisangani, Democratic Republic of Congo

[Impact de l'anémie ferriprive maternelle sur la survie du nouveau-né vulnérable de petite taille : Etude prospective à Kisangani, en République Démocratique du Congo]

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Abstract

Preventing preterm birth, small for gestational age (SGA), and low birth weight (LBW) is critical to the health of children worldwide. Preterm birth, SGA, and LBW are referred to as vulnerable small newborns or VSN. The aim of this study was to determine the survival of VSN born to mothers with iron deficiency anemia or IDA and its predictors. A prospective, matched, open-label, multicenter cohort study of 1,226 newborns of mothers with IDA. We performed statistical analysis, including competing risk analysis and Cox regression modeling, to illustrate the clinical effects of IDA on newborns and risk factors. The risk of clinical effects and the incidence rate of the PT+SGA+LBW phenotype increased by more than 2.21 times (2.20-2.21) and 3.86 times (3.82-3.90), respectively. The risk of the T+SGA+LBW phenotype increased by 1.28 times (1.28-1.29) or 28% for moderate IDA, by 2.48 times (2.47-2.49) for severe IDA. This risk increased by 5.64 times (5.63-5.66) for maternal low birth weight at the end of pregnancy. The risk associated with the PT+AGA+LBW phenotype increased by 1.78 (1.75-1.81) or 78% and by 5.53 (5.47-5.59) times in live births from mothers with low early gestational weight and from mothers without iron supplementation. Maternal iron deficiency anemia has a serious impact on newborn health. Threatened by a higher incidence of mortality and various short- and long-term morbidities, VSNs born to IDA mothers should receive appropriate care.

Keywords: Survival, vulnerable small newborn (VSN), iron deficiency anemia, prospective matched birth cohort.

Résumé

La prévention des naissances prématurées, des petits pour l'âge gestationnel (PAG ou SGA en anglais) et du faible poids de naissance (FPN ou LBW) est essentielle à la santé des enfants du monde entier. Les naissances prématurées, les SGA et les LBW sont appelés nouveau-né vulnérable de petite taille ou SVN. Le but de cette étude est de déterminer la survie du SVN né d'une mère avec anémie ferriprive ou IDA et ses facteurs prédictifs. Étude de cohorte prospective, appariée, ouverte et multicentrique portant sur 1 226 nouveau-nés de mères souffrant IDA. Nous avons réalisé une analyse statistique, incluant l'analyse concurrente de risques et le modèle de regression de Cox, pour illustrer les effets cliniques de l'IDA sur les nouveaux-nés et les facteurs de risque. Le risque d'effets cliniques et le taux d'incidence du phénotype PT+SGA+LBW ont augmenté respectivement de plus de 2,21 fois (2,20-2,21) et de 3,86 fois (3,82-3,90). Le risque du phénotype T+SGA+LBW a augmenté de 1,28 fois (1,28-1,29) ou 28 % pour l'IDA modérée, de 2,48 fois (2,47-2,49) pour l'IDA sévère. Ce risque a augmenté de 5,64 fois (5,63-5,66) pour l'insuffisance pondérale de la mère en fin de grossesse. Le risque associé au phénotype PT+AGA+LBW a augmenté de 1,78 (1,75-1,81) ou 78 % et de 5,53 fois (5,47-5,59) chez les naissances vivantes issues de mères à faible poids en début de grossesse et de mères sans supplémentation en fer. L'anémie ferriprive maternelle a un impact grave sur l'état de santé du nouveau-né. Menacés par une incidence plus élevée de mortalité et diverses morbidités à court et à long terme, les VSN issus des mères IDA devrait bénéficier de soins appropriés.

Mots-clés: Survie, nouveau-né vulnérable de petite taille (VSN), anémie ferriprive, cohorte de naissance prospective appariée.

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1. Introduction

Many newborns who experience difficulties during the intrauterine period are born prematurely or small for gestational age (SGA) and suffer from fetal growth issue, which can lead to low birth weight or LBW (Ashorn et al., 2023). Prematurity, SGA, and LBW are important clinical and health indicators for monitoring neonatal health status(Applegate et al., 2024) and are associated with stillbirths and lifelong health problems in early survivors (Ashorn et al., 2023). Premature newborns are born before 37 weeks gestational age (Martin & Osterman, 2024), while LBW newborns have a birth weight less than 2.5 kg, regardless of gestational age or smaller than expected for gestational age and sex (Cutland et al., 2017).

LBW predisposes newborns to physical and mental growth delay and premature death (Jana et al., 2023), the consequences of which can continue into adulthood, thereby increasing the risk of chronic diseases in adulthood such as obesity and diabetes (Janczewska et al., 2023). Newborns who are both premature and LBW have the highest risk of adverse neonatal outcomes (Janczewska et al., 2023). SGA newborns have low iron stores, which may increase the risk of anemia later in life(Li et al., 2022) and a risk of neonatal and post-neonatal mortality that could be 83% and 90% respectively than those of appropriate gestational age (Haksari et al., 2023).

Each year, approximately 35 million babies, more than 25% of all newborns worldwide, are born too early or too small (Huicho et al., 2024). Cajachagua-Torres et al., estimate that 23.3 million SGA newborns, 15 million preterm newborns, and 20 million LBW newborns are born each year worldwide (Cajachagua-Torres et al., 2024). In addition, WHO estimates that nearly 30 million premature or LBW newborns fall ill and are most at risk of death and disability (WHO, 2018a). South Asia and sub-Saharan Africa together account for approximately 65% of premature births (Ohuma et al., 2023), 28% and 13% of LBW cases worldwide respectively (Belay et al., 2025). The Democratic Republic of the Congo (DRC) reports nearly 12% of premature births and 10% of LBW births each year, of which 10% die from direct complications (UNICEF, 2017) (USAID/PCI, 2017). In 2017, 80% of LBW babies and 66% of preterm babies means more than 2.5 million newborns died within the first 28 days of life (UNICEF, 2018).

Preventing preterm births, SGA, and LBW is essential for the health of children worldwide (Darmstadt et al., 2023). However, progress in this area has been slow due to the delay in implementing measures to address newborn vulnerability, the lack of a broad coalition of stakeholders, and the absence of an appropriate governance structure for change (Lawn et al., 2023). Phenotypes of vulnerable newborns, combining prematurity, SGA, and LBW, provide a better scientific basis for developing national and global commitments to give newborns a healthy start in life (Ashorn et al., 2023) Thus, a new definition and conceptual framework encompassing preterm births, SGA, and LBW was proposed under the term of "vulnerable small newborn" or VSN (Ashorn et al., 2023).

VSNs are exposed to harmful issues during their intrauterine period, leading to fetal growth delay, preterm birth, or both (Ashorn et al., 2023). After birth, they have a significantly increased risk of neonatal death and subsequent infant mortality (Lawn et al., 2023). Being born too early or too small is also associated with stillbirth and multiple morbidities with negative short- and long-term consequences for newborns and their families. This represents a significant loss of human and economic capital for society. Therefore, preventing VSNs is essential for both child health and societal development (Huicho et al., 2024). The adoption of unified framework can facilitate the improvement of problem definition and programming for VSN prevention, whose preventive interventions enable live newborns to have a healthier start in life, while reducing the number of stillbirths, improving maternal health, and contributing to positive economic and social development in society (Malik et al., 2025).

It is important to determine the survival of the VSN of a mother suffering from IDA and the related predictive factors in Kisangani (DRC) where little is known about this problem. The aim of this work is to contribute to better knowledge and better policy based on scientific evidence to avoid VSN.

2. Material and Methods

2.1. Study design

The prospective, matched, open-label, multicenter cohort study was conducted in Kisangani from October 1, 2022, to June 19, 2023, preceded by a pre-survey conducted from August 13 to 29, 2022,

covered 10% of the total sample of health facilities to test the consistency of data on prenatal care and deliveries from July to September 2022 A framework for collaboration between the Ministry of Health, the NGO Ema-Esu, and the principal investigator was established for the purchase of laboratory equipment, supplies and the rental of automated equipment from the Ema-Esu laboratory. This laboratory carried out all analyses to ensure the reliability and validity of the results in accordance with the international standards.

2.2. Study population

2.2.1. Inclusion criteria

The study participants were newborns of mothers suffering with IDA who gave birth in selected health facilities in Kisangani and were followed up since registration in antenatal care. These newborns were considered as "exposed" or cases and those of mothers who did not suffering with IDA were considered as "unexposed" or control group.

2.2.2. Exclusion criteria

Newborns from multiple pregnancies of mothers suffering from IDA and those whose mothers had a history of immune or hematological diseases or blood transfusions in the last six months were excluded from the study. The same was done for seriously ill newborns transferred from other facilities for specialized care.

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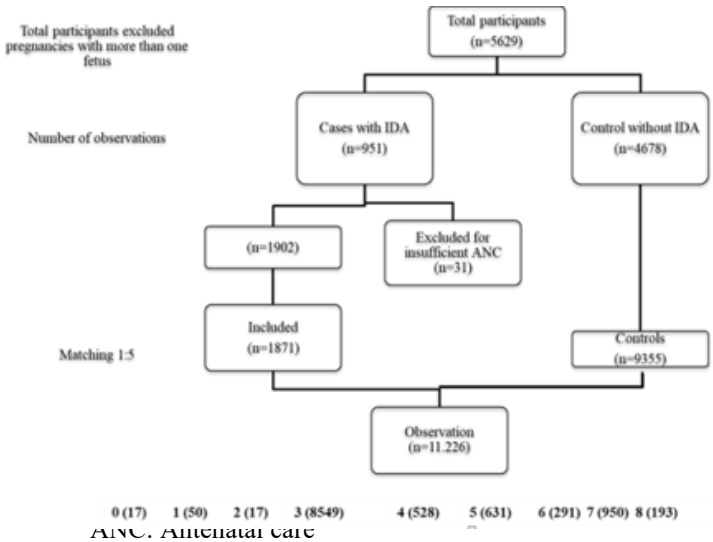
Sampling and follow-up period

Out of the 46 health facilities offering quality maternal and child healthcare services and follow-up to delivery according to American Academy of Pediatrics, 2017 and OMS 2017 (American Academy of Pediatrics, 2017; OMS, 2016), we selected 17 health facilities through a simple random survey, including 13 health centers and 4 general referral hospitals in integrated health zones in relation to refocused on antenatal care and referral delivery systems as recommended by WHO (WHO, 2018b).

To determine the sample size of newborns of mothers suffering from IDA, the "power logrank" command in Stata BE-17.0 using the Freedman method, option nratio 2 of the time spectrum and censoring was used (Machin et al., 2011). We used Liu estimates for an unbalanced 1/2 survey, with a dropout rate of 10%, a wdprob (0.1) specification, an α error of 0.05, and a correction for continuity (Liu et al., 2013). Each mother of the newborn had 66 days of prenatal care follow-up according to WHO (WHO, 2018c), with reference to the WHO's positive experience with prenatal care (WHO, 2018b), whose two sessions reflected histories of IDA in mothers (Janvin et al., 2024) and components of multiple losses during the follow-up period(Westbury et al., 2016). Out of 951 newborns in the sample with the potential to generate 1,902 observations, it was found that only 1,871 observations were recorded.

Matching was implemented using the "Matching cases and controls 1:5" format as recommended by other authors (Iwagami & Shinozaki, 2022). A control cohort was identified, and newborns of mothers who suffered from IDA during pregnancy were matched according to key variables explaining the variation in survival. The incidence of risk was used as the matching estimator, as not all newborns of mothers with iron deficiency anemia are likely to be premature, SGA, or die due to their mothers' IDA (Abu-Ouf & Jan, 2015). Thus, from 1,871 original cohort newborns, 9,355 control cohort observations were created so the total number of newborns was 11,226.



ANC: Antenatal care

IDA: Iron Deficiency anemia

2.2.3. Study outcome variables

The primary outcome of our study was SVN as defined below with three parameters. We added a fourth parameter which is survival meaning healthy survivors or died). Thus, all events were competing with each other, as the study conditions would have ended as soon as an occurrence was observed.

One of the main reasons for combining multiple types of outcomes is to collect a larger number of events in order to increase statistical power (Serdar et al., 2021). A composite endpoint was defined as the time to the first death or non-fatal event of interest and incorporated information on deaths and serious non-fatal events (Mao & Kim, 2021). The combination of these four outcomes into an "event-type" variable was estimated using the "Last Rules" method for mothers, widely used in clinical settings, based on the revised Naegele rule Loytved & Fleming, (2016) and the "Measurement of the length of newborn feet" method (Kc et al., 2015).

Newborns were classified according to nine clinical phenotypes described as follows: 1) Full-term newborns with normal weight and appropriate size for age (T+AGA+NLBW), 2) Preterm newborns with normal weight and appropriate size for age (PT+AGA+NLBW), 3) Full-term newborns with normal weight and small for age (T+SGA+NLBW), 4) Preterm newborns with normal weight and small for age (PT+SGA+NLBW), 5) Preterm newborns with low weight and appropriate for age (PT+AGA+LBW), and 6) Full-term newborns with low weight and small for age (T+SGA+LBW), 7) Preterm newborns with low weight and small for age (PT+SGA+LBW), for live births, and 8) Full-term newborns who died (T+D) and 9) Preterm stillbirths (PT+D), for deaths (Darmstadt et al., 2023).

The T+AGA+NLBW category refers to censored cases. All other categories refer to concurrent events. The analyses were stratified according to these clinical phenotypes of newborns to highlight possible patterns of perinatal diseases in order to facilitate clinical decision-making (Ruiz-Martinez et al., 2022).

Table I. Event codes for the e-type variable

		Event type	
0	Term newborns of age-appropriate size and Non-Low Birthweight	T+AGA+NLBW	Censored
1	Preterm newborns of age-appropriate size and Non-Low Birthweight	PT+AGA+NLBW	Competing event
2	Preterm newborns of age-appropriate size and Low Birthweight	PT+AGA+LBW	Competing event
3	Term newborns of small size for age and Non-Low Birthweight	T+ SGA+NLBW	Competing event
4	Preterm newborns of small size for age and Non-Low Birthweight	PT+ SGA+NLBW	Competing event
5	Term newborns of small size for age and Low	T+SGA+LBW	Competing event

Predictive variables

Predictive variables were selected based on a review of the literature. These included the sex of the newborn and predictive factors for the incidence of iron deficiency anemia during pregnancy, which are groups of newborns of mothers with iron deficiency anemia (Anubha et al., 2023), as well as birth to a mother who was underweight at both the beginning and end of pregnancy (Oklahoma State Department of Health, 2019), from mothers who did not use ITN (Mwangu et al., 2022) and did not receive iron supplements during pregnancy (Saptarini et al., 2023).

Data quality assurance procedures

Data quality was ensured through the design and testing of data collection materials, as well as through pre-training of health facility data collectors and supervisors. Appropriate modifications made after pre-test results and daily supervision by the principal investigator to review and verify completeness, accuracy and clarity of data collection materials, and next-morning corrections were implemented.

Study evaluation

The follow up was done in two periods (two times) to estimate how the iron concentration could change from the first period to the second. The first period lasted 73 days from the start of the study, from December 10, 2022, to May 12, 2023. The second period lasted 63 days, from May 15 to August 28, 2023.

The stratified cumulative incidence curves were compared using a log-rank test with an α of 0.05 to assume a statistically significant difference (Satapathy l., 2024).

Statistical analysis of survival data

Management and processing of said data

Data entry and compilation were performed using Microsoft Excel. Processing and analysis were performed using Stata/BE 17.0 (StataCorp, TX, and USA) based on data imported from Microsoft Excel. These data were edited using simple frequencies and cross-tabulations. Categorical variables were recategorized and continuous variables were categorized to suit the analysis. Proportions were used as descriptive statistics for categorical variables. Discrete data analysis was performed using Pearson's chi-square test. The declaration, description, summary, and cleaning of survival data, as well as the signaling of variables, were performed using Stata commands.

We analyzed the predictive factors for survival of SVN, premature newborns (premature birth) or small newborns (SGA) with low birth weight (LBW). We performed crude and adjusted analyses.

Statistical model

Concurrent risk analysis

Concurrent risk regression offers a useful alternative to Cox regression for survival data in the presence of concurrent risks (Zuur, 2010). Concurrent risk refers to the possibility that, instead of a recurrence of neonatal prematurity, a concurrent event occurs, such as neonatal death, which prevents the onset of prematurity and low birth weight in the newborn (Staffa & Zurakowski, 2020). The cumulative incidence function is the standard method for competing events, estimating the probability that a specific event will occur before time t when no event occurs (Sestelo et al., 2024). Since competing events are different from standard censoring, a competing risks analysis requires a new methodology and caution in interpreting the results (Austin et al., 2022). Two methods are used to obtain the risk ratio considering competing risks (Geskus, 2024a).

The cause-specific hazard function (CSH) is the most used in etiological research. It calculates the hazard ratio of patients exposed to the risk of the event in question by considering other outcomes as censored, except for the event in question, and uses event-specific Cox regression (Mansournia et al., 2022). If PT+AGA+NLBW, PT+AGA+LBW, T+SGA+NLBW, PT+SGA+NLBW, T+SGA+LBW, PT+SGA+LBW, T+D, and PT+D newborns are all considered, the CSH is the incidence of newborns who have never experienced either event.

Meanwhile, the subdistribution hazard (SDH) function is appropriate for prognostic studies (predicting an individual's risk). It was proposed by Fine and Gray and includes subjects who have experienced competing events, even if they are not exposed to the risk of the event in question. In this method, subjects who have experienced competing events are not censored but remain in the risk sets (Austin et al., 2022). The SDH for the incidence of PT+AGA+LBW, PT+AGA+LBW, T+SGA+NLBW, PT+SGA+NLBW, T+SGA+LBW, PT+SGA+LBW, T+D, and PT+D newborns is the incidence rate of newborns who are still alive or have died.

As this is an event of interest and there are several competing events, competing risk regression has been generalized (Geskus, 2024b). After defining the failure event of interest by code 1 in the stset definition of the data, competing events were defined by codes 2 to 8 in the “compete” option of stcrreg and required special attention in a competing risks regression.

The data were analyzed by estimating the cause-specific risks for each of these events. By performing the competing risks analysis at the time elapsed until the first event for each patient and the type of that event, only the time of that first event was recorded (Austin et al., 2016). As participants entered the study at different times, the variable “origin” or the start of the risk was specified (Schober & Vetter, 2018).

Taking advantage of stcrreg's treatment of importance weights (iweights) as individual frequency weights, the weight variable (wt) was set to one for patients with a single record and to one divided by the number of related events for patients with multiple records. In this way, each patient contributed to a total weight of one observation. The “vce (cluster id)” was specified to account for standard errors of correlation within multiple records for the same patient (Barratt et al., 2021).

Ethical approval

Ethical approval for this study was obtained from the ISTM Kinshasa Bioethics Committee under number 0038/CBE/ISTM/KIN/RDC/PMBBL/29.11.2023).

3. Results

3.1. General characteristics

The basic characteristics of the study were presented simultaneously in table II for the survival of mothers of newborns with iron deficiency anemia and in Table 3 for the clinical effects of maternal IDA on newborn survival. The analysis in table II covered a total of 11,226 mothers, of whom 6,297 (56.09%) had severe iron deficiency anemia, 3,660 (32.60%) had moderate iron deficiency anemia, and 1,269 (11.30%)

had sufficient iron during pregnancy. All results were statistically satisfactory. Most mothers, aged between 20 and 35 (73.13%), had a normal weight both at the beginning and end of pregnancy (50.44% and 43.06%). Many of them did not sleep under the ITNITN (71.04%) and did not receive iron supplements (67.44%) during pregnancy.

Table II. Basic characteristics related to the survival of mothers suffering from iron deficiency anemia during pregnancy

Characteristic	Total Patients	Mothers with iron-deficiency anemia IDA Severe	IDA Moderate	Sufficient iron
Patients (%)	11,226	6,297 (56.09)	3,660 (32.60)	1,269 (11.30)
Maternal BMI start				$p < 0.001$
Normal weight	5,626 (50.44)	3,229 (51.28)	1,740 (47.54)	693 (54.61)
Underweight	2,600 (23.16)	1,618 (25.69)	748 (20.44)	234 (18.44)
Overweight	2,964 (26.40)	1,450 (23.03)	1,172 (32.02)	342 (26.95)
Maternal BMI end				$p < 0.001$
Normal weight	4,834 (43.06)	2,708 (43.00)	1,510 (41.26)	616 (48.54)
Underweight	2,564 (22.84)	1,639 (26.03)	714 (19.51)	211 (16.63)
Overweight	3,828 (34.10)	1,950 (30.97)	1,436 (39.23)	442 (34.83)
Maternal ITN use				$P < 0.001$
Use	3,251 (28.96)	1,323 (21.01)	1,415 (38.66)	513 (40.43)
Don't use	7,975 (71.04)	4,974 (78.99)	2,245 (61.34)	756 (59.57)
Maternal iron intake				$P < 0.001$
Yes	3,655 (32.56)	360 (5.72)	2,302 (62.90)	993 (78.25)
No	7,571 (67.44)	5,937 (94.28)	1,358 (37.10)	276 (21.75)

The analysis of the table III covered a total of 1,226 newborns from which76.15% in the group of T+SGA+NLBW, 8.46% of T+D, 5.62% of PT+SGA+NLBW, 4.70% of SGA+T+LBW, 2.59% of PT+SGA+LBW; 1.57% of PT+D; 0.15% of T+AGA+NLBW; 0.60% of PT+AGA+NLBW; and 0.15% of PT+AGA+LBW.

The $\chi 2$ test revealed a significant difference in the clinical effects of maternal iron deficiency anemia on newborn survival. Newborn age and maternal age, iron deficiency anemia, the circular mass index at both the beginning and end of pregnancy, marital status and the mother's health consultation area, use of ITN, and iron supplementation by the mother were very significantly associated with the clinical effects of maternal iron deficiency anemia ($p < 0.001$).

There were 53.87%girls versus 46.13%, of boys, with 100% of T+AGA+NLBW newborns, 46.74% of D+T, 69.89% of D+PT, 25.37% of PT+AGA+NLBW, 54.22% of T+SGA+NLBW, 49.29% of PT+SGA+NLBW, 100% of PT+AGA+LBW, 57.58% of T+SGA+LBW, and 61.51% of PT+SGA+LBW.

Newborns from mothers who suffered from severe IDA were more numerous, at 56.09%, with 100% of T+AGA+NLBW, 83.05% of T+D, 67.05% of PT+D, 5.97% of PT+AGA+NLBW, 52.24% of T+SGA+NLBW, 47.07% of PT+SGA+NLBW, 23.53% of PT+AGA+LBW, 77.27% of T+SGA+LBW, and 66.67% of PT+SGA+LBW.

Newborns from mothers who had a normal weight at both the beginning and the end of pregnancy were50.44% and 43.06% respectively with 47.06% of T+AGA+NLBW, 17.37% and 8.32% of D+T, 18.75% and 13.07% of D+PT, 59.70% of PT+AGA+NLBW, 53.64% and 46.50% of T+SGA+NLBW, 64.03% and 50.40% of PT+SGA+NLBW, 58.82% of PT+AGA+LBW, 51.33% and 46.59% of T+SGA+LBW, and 49.83% and 46.39% of PT+SGA+LBW.

Newborns whose mothers did not sleep under ITN were 71.04% distributed as follow: 100% for T+AGA+NLBW, 75.89% for T+D, 84.66% for PT+D, 74.63% of PT+AGA+NLBW, 68.20% of T+SGA+NLBW, 71.95% of PT+SGA+NLBW, 100% of PT+AGA+LBW, 89.02% of T+SGA+LBW, and 91.75% of PT+SGA+LBW.

Newborns from mothers who did not receive iron supplementation were 67.44% distributed as follow: 100% of T+AGA+NLBW, 87.37% of T+D, 77.27% of PT+D, 46.27% of PT+AGA+NLBW, 63.66% of T+SGA+NLBW, 64.18% of PT+SGA+NLBW, 82.35% of PT+AGA+LBW, 82.39% of T+SGA+LBW, and 89.69% of PT+SGA+LBW.

Table III. Baseline characteristics of the clinical effects of matern vulnerable small newborn

Characteristic	Total Patients	T+AGA+NLBW	PT+AGA+NLBW	PT+AGA+LBW	T+SGA+NLBW
Patients (%)	11,226	17 (0.15)	50 (0.45)	17 (0.15)	8,549 (76.15)
Newborn's sex					
Boy	5,179 (46.13)	0 (0.00)	35 (70.00)	0 (0.00)	3,914 (45.78)
Girl	6,047 (53.87)	17 (100.00)	15 (30.00)	17 (100.00)	4,635 (54.22)
Maternal IDA					
Sufficient iron	1,269 (11.30)	0 (0.00)	11 (22.00)	10 (58.82)	1,048 (12.26)
IDA Moderate	3,660 (32.60)	0 (0.00)	35 (70.00)	3 (17.65)	3,035 (35.50)
IDA Severe	6,297 (56.09)	17 (100.00)	4 (8.00)	4 (23.53)	4,466 (52.24)
Maternal BMI start					
Normal weight	5,662 (50.44)	8 (47.06)	30 (60.00)	10 (58.82)	4,586 (53.64)
Underweight	2,600 (23.16)	0 (0.00)	0 (0.00)	7 (41.18)	1,210 (14.15)
Overweight	2,964 (26.40)	9 (52.94)	20 (40.00)	0 (0.00)	2,753 (32.20)
Maternal BMI end					
Normal weight	4,834 (43.06)	8 (47.06)	30 (60.00)	10 (58.82)	3,975 (46.50)

Incidence of clinical phenotypes in newborns of mothers with iron deficiency anemia

The table IV shown the incidence rates of clinical phenotypes of newborns from mothers with IDA.

The incidence of clinical phenotypes was 0.63% (95% CI: 0.62, 0.65) for all newborns of mothers with IDA overall. The group of AGA+PT+LBW had the incidence of 1.04% (95% CI: 0.65, 1.68), while the SGA+T+NLBW group had an incidence of 0.61% (95% CI: 0.59, 0.62).

The incidence of clinical phenotypes was 0.63% (95% CI: 0.65, 0.68) found in newborns of mothers with severe IDA in general. This incidence in the AGA+PT+LBW group was 1.18% (95% CI: 0.65, 3.13), while in SGA+T+NLBW group, it was 0.63% (95% CI: 0.61, 0.65).

Overall, the incidence was 0.66% (95% CI: 0.64, 0.69) and 0.67% (95% CI: 0.64, 0.69) for newborns of mothers who were underweight at both the beginning and end of pregnancy respectively. In the group of AGA+PT+LBW, this incidence was 1.11% (95% CI: 0.53, 2.34), while in SGA+T+NLBW was 0.62% (95% CI: 0.58, 0.65) and 0.61% (95% CI: 0.58, 0.65).

About ITN, newborns from mothers who did not sleep under ITN had an incidence rate of 0.64% (95% CI: 0.63, 0.66) overall. In the AGA+PT+LBW group it was 1.04% (95% CI: 0.53, 1.68), while D+PT group had an incidence rate of 0.37% (95% CI: 0.33, 0.40).

Concerning the iron supplementation during the ANC, newborns from mothers who did not get the iron during pregnancy had an incidence rate of 0.66% (95% CI: 0.64, 0.67). For the AGA+PT+LBW, the incidence was 1.04% (95% CI: 0.62, 1.76), while SGA+T+NLBW had 0.63% (95% CI: 0.56, 0.64).

Cumulative incidence

The analysis of the cumulative incidence of different vulnerable phenotypes in newborns from mothers with IDA is derived from the cumulative risk function of the Cox Model (Kalbfleisch & Schaubel, 2023) and the CIF, respectively, as illustrated in the figures below. Thus, the Cox model's cumulative risk estimate is generally higher than the corresponding estimate derived from the CIF. The extended shift between these two estimates is illustrated in the figures.

Table IV. Incidence rate of clinical effects of maternal iro

Exposure	Total Patients			PT+AGA+NLBW			
	Events (clinical effects)	P-T (day)	Events/P-T100 (95%CI)	NC	P-T	NC/P-T100 (95%CI)	NC
Patients	11,209	1,769,322	0.63 (0.62, 0.65)	67	6,901	0.97 (0.76, 1.23)	8,549
Newborn sex							
Boy	5,179	815,582	0.64 (0.62, 0.65)	50	4,981	1.00 (0.76, 1.32)	3,914
Girl	6,030	953,740	0.63 (0.62, 0.65)	1 7	1,920	0.89 (0.55, 1.42)	4,635
Maternal IDA							
Sufficient iron	1,269	217,745	0.58 (0.55, 0.62)	11	1,242	0.89 (0.49, 1.60)	1,048
IDA Moderate	3,660	602,016	**0.61 (0.59, 0.63)**	52	5,203	1.00 (0.76, 1.31)	3,035
IDA Severe	6,280	949,561	**0.63 (0.65, 0.68)**	4	456	0.88 (0.33, 2.34)	4,466
Maternal BMI start	5,654	889,585	0.64 (0.62, 0.65)	40	3,614	1.11 (0.81, 1.51)	4,586
Normal weight	2,600	393,274	**0.66 (0.64, 0.69)**	0		0.00	1,210
Underweight	2,955	486,463	**0.61 (0.59, 0.63)**	27	3,287	0.81 (0.56, 1.20)	2,753
Overweight							
Maternal BMI							

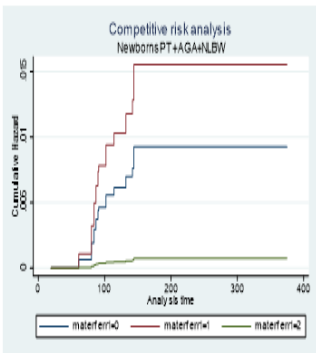
Legend: NC: New case; P-T: Person-time (day)

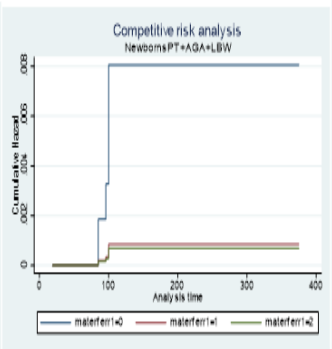
Table V. Results of multivariate modeling of cause-specific risk (CSH approach) and Fine and Gray

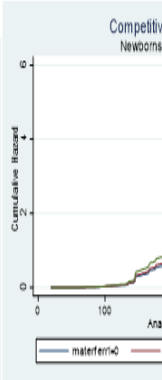
	PT+AGA+NLBW				PT+AGA+LBW				T+SGA+NLBW			
Predictor	Adjusted HRcs	p	Adjusted SHR	p	Adjusted HRcs	P	Adjusted SHR	p	Adjusted HRcs	p	Adjusted SHR	p
Newborn sex												
Girl	0.53 (0.53-0.54)	0.000	0.56 (0.55-0.57)	0.000	1.45e+17		1.69e+11	0.000	0.94 (0.94-0.94)	0.000	0.95 (0.95-0.95)	0.000
Maternal IDA												
IDA Moderate	1.83 (1.81-1.84)	0.000	1.69 (1.66-1.72)	0.000	0.14 (0.14-0.15)	0.000	0.15 (0.14-0.15)	0.000	1.10 (1.10-1.10)	0.000	1.14 (1.14-1.14)	0.000
IDA Severe	0.11 (0.11-0.11)	0.000	0.09 (0.08-0.09)	0.000	0.05 (0.04-0.05)	0.000	0.04 (0.04-0.04)	0.000	1.38 (1.37-1.38)	0.000	1.37 (1.37-1.37)	0.000
Maternal BMI start												
Underweight	5.51e-15	1.000	1.30e-10	0.000	1.78 (1.75-1.81)	0.000	1.28 (1.26-1.30)	0.000	1.33 (1.32- 1.33)	0.000	1.62 (1.62-1.63)	0.000
Overweight	3.33 (3.33-3.38)	0.000	4.45 (4.40-4.50)	0.000	0.39	1.000	0.66 (0.66- 0.67)	0.000	1.05 (1.05-1.05)	0.000	1.08 (1.07-1.08)	0.000
Maternal BMI end												
Underweight	7.38e-15	1.000	2.08e-10	0.000	1.22 (1.20-1.24)	0.000	1.31 (1.29-1.34)	0.000	0.44 (0.44-0.44)	0.000	0.22 (0.22-0.22)	0.000
Overweight	0.27 (0.26-0.27)	0.000	0.21 (0.21-0.21)	0.000	1.10e-18	1.000	7.65e-12	0.000	0.98 (0.98-0.98)	0.000	1.25 (1.25-1.25)	0.000
Maternal ITN use												
Don't use	0.87 (0.86-0.87)	0.000	0.82 (0.81-0.84)	0.000	4.75e+16		1.54e+11	0.000	1.00 (1.00-1.00)	0.000	0.86 (0.85-0.86)	0.000
Maternal ITN use												
No	1.90 (1.89-1.91)	0.000	1.87 (1.84-1.90)	0.000	5.53 (5.47-5.59)	0.000	3.95 (3.81-4.10)	0.000	1.10 (1.10-1.10)	0.000	0.90 (0.90-0.90)	0.000

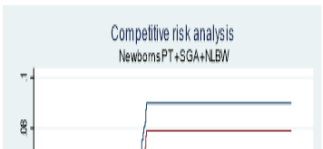
	T+SGA+LBW				PT+SGA+NLBW		
Predictor	Adjusted HRcs	p	Adjusted SHR	p	Adjusted HRcs	p	Adjus
Newborn sex							
Girl	1.40 (1.40-1.40)	0.000	1.20 (1.19-1.21)	0.000	0.73 (0.73-0.73)	0.000	0.72 (
Maternal IDA							
IDA Moderate	1.28 (1.28-1.29)	0.000	1.08 (1.08-1.09)	0.000	0.94 (0.94-0.94)	0.000	0.88 (
IDA Severe	2.48 (2.47-2.49)	0.000	2.10 (2.08-2.12)	0.000	0.60 (0.60-0.60)	0.000	0.53 (
Maternal BMI start							
Underweight	0.33 (0.33-0.33)	0.000	0.41 (0.40-0.41)	0.000	0.47 (0.47-0.47)	0.000	0.49 (
Overweight	1.61 (1.59-1. 64)	0.000	1.35 (1.33-1. 37)	0.000	0.55 (0.55-0.55)	0.000	0.53 (
Maternal BMI end							
Underweight	5.64 (5.63-5.66)	0.000	4.68 (4.62-4.73)	0.000	0.62 (0.62-0.63)	0.000	0.54 (
Overweight	0.01 (0.01-0.01)	0.000	0.01 (0.01-0.01)	0.000	1.37 (1.37-1.37)	0.000	1.50 (
Maternal ITN use							
Don't use	3.78 (3.77-3.79)	0.000	3.60 (3.57-3.62)	0.000	1.10 (1.09-1.10)	0.000	1.03 (
Maternal iron							
No	1.22 (1.22-1.22)	0.000	1.03 (1.02-1.03)	0.000	1.44 (1.44-1.44)	0.000	1.28 (

	D+T				D+PT			
Predictor	**Adjusted HRcs**	**p**	**Adjusted SHR**	**P**	**Adjusted HRcs**	**p**	**Adjusted SHR**	**p**
Newborn sex								
Boy	1		1		1		1	
Girl	1.02 (1.01-1.02)	**0.000**	0.79 (0.79-0.79)	**0.000**	1.95 (1.94-1.95)	**0.000**	1.90 (1.89-1.91)	**0.000**
Maternal IDA								
IDA Moderate	11.16 (11.06-11.26)	**0.000**	10.54 (10.38-10.71)	**0.000**	1.48 (1.47-1.48)	**0.000**	1.47 (1.45-1.49)	**0.000**
IDA Severe	23.73 (23.51-23.94)	**0.000**	19.02 (18.73-19.32)	**0.000**	1.22 (1.21-1.23)	**0.000**	1.06 (1.05-1.07)	**0.000**
Maternal BMI start								
Underweight	1.06 (1.06-1.06)	**0.000**	0.62 (0.62-0.62)	**0.000**	1.13 (1.12-1.13)	**0.000**	1.28 (1.27-1.30)	**0.000**
Overweight	8.12e-24		1.51e-13	**0.000**	3.77 (3.70-3.84)	**0.000**	4.26 (4.21-4.31)	**0.000**
Maternal BMI end								
Underweight	15.11 (15.07-15.15)	**0.000**	25.68 (25.46-25.90)	**0.000**	5.05 (5.02-5.08)	**0.000**	4.44 (4.39-4.49)	**0.000**
Overweight	1.32e-25		2.58e-15	**0.000**	0.03 (0.03-0.04)	1.000	0.03 (0.03-0.04)	**0.000**
Maternal ITN use								
Don't use	1.11 (1.11-1.12)	**0.000**	0.76 (0.76-0.76)	**0.000**	4.76 (4.74-4.78)	**0.000**	4.11 (4.06-4.15)	**0.000**
Maternal iron use								
No	2.71 (2.70-2.72)	**0.000**	2.51 (2.49-2.53)	**0.000**	1.10 (1.10-1.11)	**0.000**	1.00 (0.99-1.01)	0.216

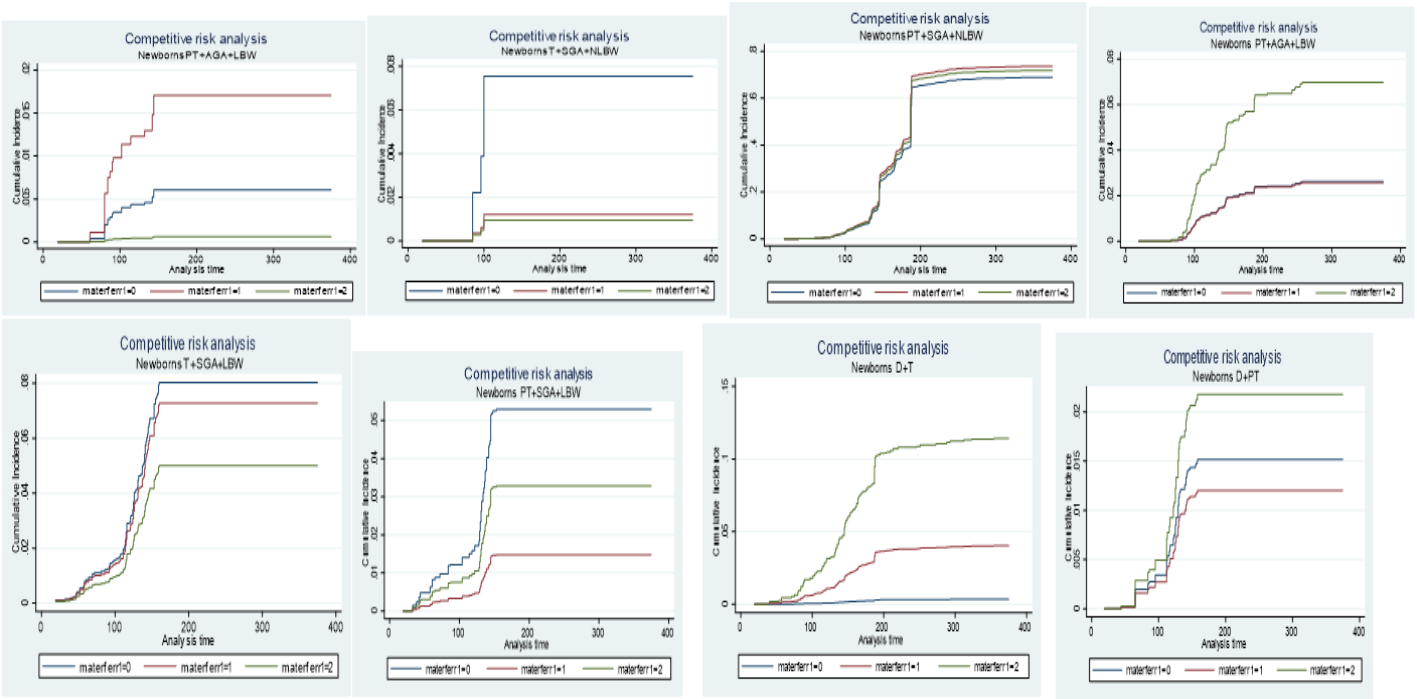








Figures 2. Estimated cumulative incidences for HRCS



Figures 3. Estimated cumulative incidences for HR_{SD}

The risk of the PT+SGA+LBW phenotype increased more than 2.21-fold in girls, while the incidence of the PT+AGA+NLBW phenotype decreased by more than 44%. The risk of death among premature infants increased by more than 95% among girls, while the risk of death among full-term newborns increased by only more than 2%.

The risk of the T+SGA+LBW phenotype increased by more than 28% and 2.48 times, respectively, among live newborns of mothers with

moderate and severe iron deficiency anemia during pregnancy, while the incidence and risk of the PT+AGA+LBW phenotype decreased by more than 85% and 95%, respectively. While the risk of death in full-term newborns of mothers with moderate and severe iron deficiency anemia during pregnancy increased by more than 11.16 and 23.73 times, respectively, the risk in premature infants increased by only more than 48 and 22%, respectively.

The risk of the PT+AGA+LBW phenotype increased by more than 78% in live newborns of mothers who were underweight at the beginning of pregnancy, while the incidence of the T+SGA+LBW phenotype decreased by more than 59%. While the death rate among premature babies increased by more than 28%, the risk increased by only more than 6%. The risk of the T+SGA+LBW phenotype increased by more than 5.64 times the number of live births from mothers who were underweight at the end of pregnancy, while that of the T+SGA+NLBW phenotype decreased by more than 56%. While the death rate among full-term newborns increased by more than 25.68 times, the risk of death among premature babies increased by only more than 5.05 times.

The incidence of the PT+SGA+LBW phenotype increased more than 3.86 times among live newborns of mothers who did not use ITN during pregnancy, while the risk of the PT+AGA+NLBW phenotype decreased by more than 13%. While the risk of death among premature infants increased more than 4.76-fold, the risk among full-term infants increased only more than 11%.

The risk of the PT+AGA+LBW phenotype increased more than 5.53-fold among live births to mothers who did not receive iron supplementation during pregnancy, while the risk of developing the T+SGA+NLBW phenotype decreased by more than 10%. While the risk of death among full-term newborns increased more than 2.71 times, that of premature newborns increased only more than 10%.

4. Discussion

IDA in pregnant women is the most common nutritional problem, affecting around 50% of pregnant women in developing countries (Dewey et al., 2024). It occurs both in the late stages and early stages of pregnancy, when iron reserves are relatively adequate (WHO, 2020). Given the insufficient capacity of the placental iron transfer system to maintain transfer to the fetus (Georgieff et al., 2019), a mother with severe anemia is at greater risk of dying in childbirth, giving birth to a stillborn baby, or losing her child at birth. Her newborn also has an increased risk of being born prematurely or with insufficient weight and/or suffering from cognitive disorders later in life (Georgieff, 2023).

A cohort study is an observational and longitudinal study design in which each event is recorded and the incidence and risk factors of maternal iron deficiency anemia are examined (CDC, 2022). In clinical research, cohort studies are appropriate because there is reasonable evidence of an association between exposure and outcome, including the time interval between exposure and the development of the outcome (Yang et al., 2024). Prospective collection of biomarker data avoids information bias in retrospective data and selection bias due to erroneous sampling of base populations (Brien et al., 2023). Since cohort study results are often attributed to confounding factors rather than identified effects (Norgaard et al., 2017), matching reduces confounding and improves the likelihood that controls represent cases if they had not been exposed (Howards, 2018). Case selection by matching is transparent, reproducible, and protects the research from criticism that cases were intentionally chosen to bias the results (Nielsen, 2016).

This study reveals evidence of SVN in a study conducted in the FOSA of Kisangani, DRC. The overall incidence of SVN was 0.63%. The PT+AGA+LBW newborn category was the most significant, both for the overall incidence of 1.04% and for newborns of mothers with severe iron deficiency anemia, at 1.18%, newborns of mothers who were underweight at both the beginning and end of pregnancy, at 1.11%, newborns of mothers who did not sleep under ITN, at 1.04%, and newborns of mothers who did not receive iron supplementation during pregnancy, at 1.04%.

The PT+SGA+LBW phenotypes, with increases of more than 2.21 times in girls and more than 3.86 times in live births to mothers who did not use ITN during pregnancy; T+SGA+LBW, with increases of more than 28% and 2.48 times, respectively, in live births to mothers with moderate and severe iron deficiency anemia during pregnancy; more than 5.64 times in live births to mothers who were underweight at the end of pregnancy and more than 3.86 times in live births to mothers who did not use ITN during pregnancy; as well as PT+AGA+LBW, with increases of more than 78% among live births to mothers who were underweight at the beginning of pregnancy and more than 5.53 times among live births to mothers who

did not receive iron supplementation during pregnancy, are the most notable of the VSNs. Chawanpaiboon et al. identify prematurity as the leading cause of death among children under 5 worldwide and estimate that, although pre-birth survival rates have increased in high-income countries, premature newborns still die due to a lack of adequate care in many low- and middle-income countries (Chawanpaiboon et al., 2019). For its part, the WHO estimates that approximately 45% of children under five who die are newborns, 60 to 80% of whom are PT+SGA+LBW. These children have a mortality risk that is 2 to 10 times higher than their full-term and NLBW counterparts. Despite considerable progress over the past decade, the survival, health, growth, and neurological development of PT+SGA+LBW remain a concern in many countries (World Health Organisation, 2022). For their part, I. Janczewska, J. Wierzba, A. Janczewska et al. believe that premature and low birthweight children are at risk of growth disorders in early childhood, which can lead to obesity and, later, to alterations in blood pressure and other chronic cardiometabolic complications throughout childhood and adolescence into adulthood. Therefore, early and long-term clinical follow-up of patients born prematurely is necessary for the early detection and monitoring of disorders contributing to the development of metabolic syndrome and cardiovascular disease later in life (Janczewska et al., 2023).

The most significant risk factors for VSN are maternal iron deficiency anemia, maternal nutrition, non-use of ITN, and lack of iron supplementation by the mother during pregnancy.

Moderate and severe iron deficiency anemia during pregnancy increased the risk of live births with T+SGA+LBW by more than 28% and 2.48 times, respectively. It is recognized that iron deficiency anemia during pregnancy increases the risk of VSN (Obianeli et al., 2024). This situation corroborates with results from India reporting that anemia diagnosed at any time during pregnancy is associated with a 38% increased risk of VSN (Thiruvengadam et al., 2024), but contradicts those of the PRISMA study in Pakistan, where the predictive factor is not statistically significant for VSN or its categories (Malik et al., 2025). Iron deficiency anemia affects fetal development and persists in the long term, while mild or severe anemia during pregnancy leads to premature birth, maternal and infant mortality, hemorrhage, and infectious diseases (Ruiz de Vinaspre-Hernandez et al., 2025).

Underweight status at both the beginning and end of pregnancy increased the risk of live births developing PT+AGA+LBW and T+SGA+LBW phenotypes by more than 78% and 5.64 times, respectively. Maternal nutrition is an important indicator during pregnancy, influencing both maternal and fetal outcomes (Thiruvengadam et al., 2024). It is recognized that maternal malnutrition increases the risk of SVN (Dewey et al., 2024). The more severe the maternal malnutrition, the greater the adjusted risk of SGA (Salihu et al., 2021).

The following results highlight the importance of prioritizing maternal nutrition during the preconception and pregnancy periods to improve neonatal outcomes. The implementation of the WHO package of antenatal care estimated by Hofmeyer et al. (2023) (Hofmeyr et al., 2023), including multiple micronutrient supplements and protein energy balance, can prevent up to five million LBW births per year and a 15% reduction in the risk of LBW proposed by the WINGS trial (Taneja et al., 2022), by assessing the effect of the package of preconception interventions in health, nutrition, psychosocial care, and WASH.

The non-use of ITN by the mother during pregnancy increased the incidence of live births PT+SGA+LBW by more than 3.86 times. Malaria during pregnancy significantly increases the risk of LBW, preterm birth, and SGA, highlighting the need for effective malaria prevention and treatment strategies in endemic areas (Satapathy et al., 2024). In sub-Saharan Africa, pregnant women, fetuses, and newborns are all at risk of malaria infection. The use of ITN is one of the most effective methods of preventing malaria in pregnant women (Terefe et al., 2023). Data on insecticide-treated mosquito nets show an effect on premature births and low birth weight children (Osborne & Bangura, 2024). The use of an ITN and taking at least three doses of IPT during pregnancy are associated with a healthy birth weight. The number of IPT doses received during prenatal care is associated with the mother's hemoglobin level in the third trimester of pregnancy (Kabalu et al., 2024).

The lack of iron supplementation in mothers during pregnancy increased the risk of live newborns developing the PT+SGA+LBW phenotype by more than 5.22 times. The lack of iron supplementation in mothers during pregnancy increases the risk to

newborns (Ataide et al., 2023). The effect of iron supplementation during pregnancy on birth outcomes varies depending on the maternal genetic makeup related to iron metabolism (Liu et al., 2023). The metabolic process of iron occurs in oxygen transport and energy production. Low iron levels during pregnancy lead to anemia, which is associated with an increased risk of disease in the mother and fetus (Sungkar, 2021). Evidence on multiple micronutrient supplementation compared to iron and folic acid supplementation shows an effect on LBW births, SGA births, and stillbirths (Caniglia et al., 2022). Iron supplementation adjusted to the initial hemoglobin levels of non-anemic pregnant women appears to have a positive effect on fetal development, regardless of the dose. However, excessive doses of iron appear to have a negative influence on optimal fetal growth (Diaz-Torres et al., 2024).

Prenatal care is essential for the health of both mother and baby, and access to and quality of care can have a significant impact on outcomes. This includes factors such as ensuring an adequate number of prenatal visits, adherence to clinical guidelines, and the availability of necessary resources, such as basic supplies and healthcare professionals. Factors such as cultural beliefs, education, and economic status can also influence access to and quality of care (Dioses Fernández et al., 2023).

Kangaroo care, also known as kangaroo maternal care, is a method of infant care that emphasizes skin-to-skin contact between a parent and a baby and exclusive breastfeeding, particularly for premature or low birth weight infants. The baby, who is usually dressed only in a diaper and a hat, is placed in an upright position against the parent's bare chest, mimicking a kangaroo's pouch. A blanket is often used to keep the baby warm (Campbell-Yeo et al., 2015).

The kangaroo mother care method helps reduce the frequency of apnea (breathing pauses) and bradycardia (slowing of the heart rate) and can also help manage pain during minor medical procedures. Babies tend to sleep more deeply and for longer periods when in skin-to-skin contact (Kirbaş et al., 2024). This kangaroo mother care method reduces the incidence of nosocomial infections. Proximity and easy access to the breast promote more frequent and effective breastfeeding. Babies who benefit from the kangaroo mother care method often have shorter hospital stays. Constant physical contact provides a sense of security and comfort (Sema, 2024). The kangaroo mother care method promotes the establishment of a strong bond between parent and child. It promotes a deep emotional bond and attachment between parent and baby. Parents feel more confident and competent in caring for their fragile child. For mothers, skin-to-skin contact helps stimulate and maintain good milk production, which promotes successful breastfeeding (Bharadwaj & Iqbal, 2024).

Early initiation of breastfeeding is ideally recommended within one hour of the newborn's birth, a critical period often referred to as the “golden hour” due to its immense benefits for both mother and child (NHS, 2024). Colostrum, or “liquid gold,” is vital for the health and immunity of the newborn. Produced by the mother after birth, it is full of antibodies, nutrients, and growth factors that protect against infections such as sepsis, pneumonia, and diarrhea. Early breastfeeding ensures that the baby receives this crucial liquid gold, which is their first vaccine (Duale et al., 2022).

Neonatal intensive care units (NICUs), specialized healthcare facilities providing critical care to newborns, particularly premature infants or those with significant medical complications, are equipped with state-of-the-art technology and highly skilled healthcare professionals to improve survival rates and outcomes for vulnerable infants (Ava, 2024). The increased availability of these units is linked to higher admission rates, particularly of infants who are not seriously ill, and a significant reduction in mortality among vulnerable newborns, also leading to an increase in the number of admissions of infants who could previously have been cared for without intensive care (Gebrhud Berihu Haile, 2025). In countries such as the United States, admission rates to neonatal intensive care are on the rise. Between 2016 and 2023, the percentage of infants admitted to a neonatal intensive care unit in the United States increased by 13%. This trend is observed across different maternal age groups, racial/ethnic groups, gestational ages, and birth weight categories (Martin & Osterman, 2025).

Although numerous studies show the link between maternal anemia and negative outcomes, more robust research, particularly randomized controlled trials (RCTs), is needed to confirm the effectiveness of oral iron supplementation in preventing severe iron deficiency anemia and its complications. This higher-quality evidence is essential for establishing a causal relationship between interventions and improved outcomes (Watt et al., 2025)..

5. Conclusion

Maternal health has a profound impact on the health of the newborn. Pregnancy is a period of increased healthcare utilization, so addressing multiple modifiable risk factors during prenatal care is an opportunity to improve the health of both mother and newborn.

There is an urgent need to develop and implement effective and scalable prevention strategies to reduce the risk of SVN birth, which are effective, feasible, scalable, and sustainable strategies needed to address the burden of disease on SNBs in resource-limited settings. Priority should be given to combined interventions to address multifaceted modifiable risks during pregnancy. Targeting factors such as poor IDA, maternal nutrition, inflammation, and infections with simple combined regimens of routine prenatal care has proven to be highly beneficial. Supplementation in Iron during the pregnancy is strongly recommended during the ANC including the use of ITN.

Threatened by higher rates of mortality and various short- and long-term morbidities, small-for-gestational-age (SGA) newborns, who require continuous, high-quality care, must receive significant care in resource-limited areas such as Kisangani, often involving multiple parties (health professionals from different disciplines, caregivers, and families).

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Competing interests

The authors declare that they have no competing interests.

Ethical consideration

The primary data for this study come from the survey, which was approved by the Superior Institute of Technical Medicine of Kinshasa Bioethics Committee under number 0038/CBE/ISTM/KIN/RDC/PMBBL/29.11.2023). All methods were applied in accordance with current guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

Author's contributions

M.A.S: conceived and designed the study, carried out the data analysis and interpretation, and participated in the literature review and writing of the article.

P-L participated in study design, literature review, and interpretation of results and writing of the article.

J.K.-L participated in the literature review, interpretation of results and writing of the article. SB participated in the interpretation of the results. All authors performed critical revisions for important intellectual content and read and approved the final manuscript

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