UiT The Arctic University of Norway

Faculty of Health Sciences

Maternal death and maternal morbidity in Georgia

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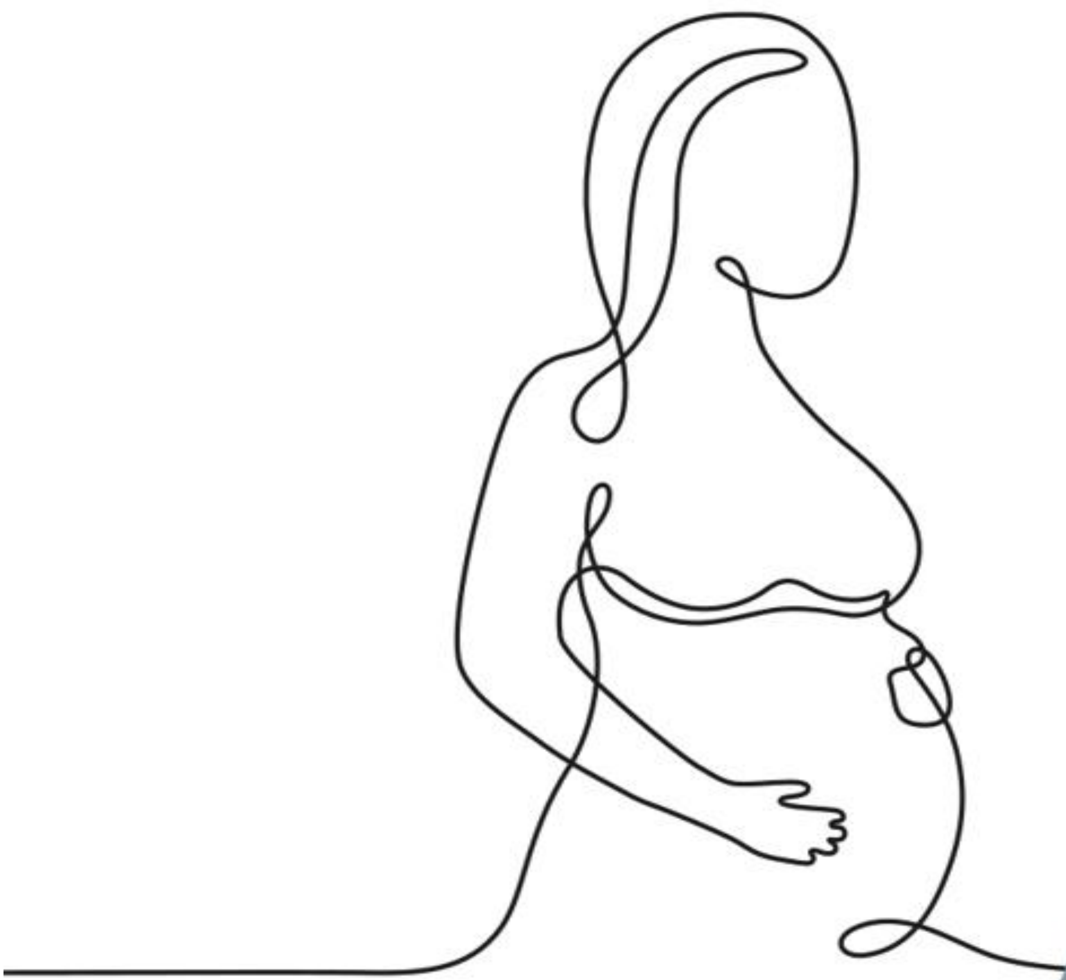

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“*Maternal mortality and morbidity is a serious crisis and one that endangers both public health and economic growth, which means everyone is impacted by it. Because just think about it: Mothers are the backbone of our economy…we must do everything we can to protect and to strengthen both maternal health and reproductive health.*”

Kamala Devi Harris, vice president of the United States under President Joe Biden

White House Day of Action on Maternal Health, 2021

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Ultimately, all my efforts are dedicated to the health of mothers, both here in Georgia and worldwide, with the goal of nurturing a healthy future generation!

Tbilisi, Georgia

May 9, 2024

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1 Abbreviations

ANC – Antenatal care

BMI – Body mass index

CEMD – Confidential Enquiry into Maternal Death

CI – Confidence interval

COVID-19 – Coronavirus disease 2019

CS – Caesarean section

DAG – Directed acyclic graph

EIDSS – electronic integrated disease surveillance system

GA – Gestational age

GBR – Georgian Birth Registry

GDP – Gross Domestic Product

ICD 10 – International Statistical Classification of Diseases and Related Health Problems, 10^{th} Revision

ICU – Intensive care unit

ID – Identity document

LMICs – Low- and Middle-Income Countries

MCHCC – Maternal and Children's Health Coordinating Committee

MD – Maternal death

MDG – Millenium Development Goals

MM – Maternal mortality

MoH – Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs of Georgia

NCDC – National Center for Disease Control and Public Health of Georgia

PPH – Postpartum hemorrhage

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

SDG – Sustainable Development Goals

RAMOS – Reproductive age mortality study

UHC – Universal health care

UN – United Nations

UNICEF – United Nations International Children's Emergency Fund

U.S. – United States

VRS – Vital registration system

WHO – World Health Organization

2 Definitions

Anemia during pregnancy: hemoglobin (Hb) level below 110 g/L (1, 2, 3).

Comorbidity: a disease or medical condition that is simultaneously present with another disease or medical condition in a patient (3, 4).

Direct obstetric maternal death: Deaths due to obstetric complications of the pregnant state (pregnancy, labor, and puerperium), as well as due to interventions, omissions, incorrect treatment, etc.

Indirect obstetric maternal death: deaths due to previous existing diseases or diseases that developed during pregnancy and did not result from direct obstetric causes but were aggravated by the physiologic effects of pregnancy (1).

Live birth: the complete expulsion or extraction of a product of conception from its mother, irrespective of the pregnancy duration, which, following separation, breathes or shows any other evidence of life such as heartbeat, pulsation of the umbilical cord, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut or the placenta is attached (1).

Maternal death (MD): the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from unintentional or incidental causes (1, 3).

Maternal health: The health of mothers during pregnancy, childbirth, and the postnatal period (3, 4).

Maternal morbidity: any health condition attributed to and/or aggravated by pregnancy and childbirth that negatively affects the woman's well-being (1, 5).

Maternal mortality: The annual number of female deaths from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes) during pregnancy and childbirth or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy. In some official sources and studies, the MM and MD are used synonymously (1).

Maternal mortality ratio (MMR): numerically shows the MDs during a given time period per 100,000 live births during the same time period (1, 2).

Post-delivery Intensive Care Unit (ICU) admission: any admission to the ICU within or outside the location of the birth facility after delivery (1, 2).

Postpartum hemorrhage (PPH): commonly defined as blood loss ≥500 ml within 24 hours after birth (1, 2, 3).

Preterm delivery: delivery before gestational week 37 (1, 2)

Severe maternal morbidity: unexpected outcomes of labor and delivery that require ICU admission and result in significant short- or long-term health effects. It also can be termed as near-miss mortality. Without identification and treatment, these conditions may result in MD (2, 3).

This thesis is based on the following papers:

I. Skhvitaridze N, Anda EE, Brenn T, Kintraia N, Gamkrelidze A. Scoping maternal care through the lens of maternal deaths: A retrospective analysis of maternal mortality in Georgia. Sex Reprod Healthc. 2020 Dec;26:100560. doi: 10.1016/j.srhc.2020.100560. Epub 2020 Oct 1. PMID: 33059117

II. Skhvitaridze N, Gamkrelidze A, Manjavidze T. Brenn T. Rylander C. SARS-CoV-2 infection during pregnancy and the risk of adverse maternal outcomes in the Republic of Georgia: a national birth registry-based cohort study. BMC Pregnancy Childbirth 24, 156 (2024). https://doi.org/10.1186/s12884-024-06329-x

III. Skhvitaridze N, Gamkrelidze A, Manjavidze T. Brenn T. Anda EE. Rylander C. Anemia during pregnancy and adverse maternal outcomes in Georgia – a birth registry-based cohort study. PLOS ONE. Submitted.

3 Abstract

Background: Maternal death (MD) and morbidity are crucial assessment indicators for the health of a nation and healthcare system development. Currently, few studies have used data from national surveillance systems to address maternal health in Georgia. This study aimed to investigate MD, maternal morbidity, and their related risk factors using data from the Georgian Birth Registry (GBR) and other national digital health surveillance systems.

Methods: Data were extracted from the GBR and other national digital health surveillance systems. Paper I, which applied a case series design, included 61 MDs from 2014 to 2017 and sought to identify direct and indirect causes of MD in Georgia. Paper II was a retrospective, registry-based cohort study of 111,493 women registered in the GBR between 2020 and 2022, and it sought to evaluate the odds of MD, post-delivery intensive care unit (ICU) admission, and caesarian section (CS) with respect to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection during pregnancy. Similarly, Paper III was a retrospective, registry-based cohort study that included 129,959 participants registered to the GBR between 2019 and 2022. Paper III sought to investigate the national and regional prevalence of maternal anemia in Georgia as well as to evaluate the relationships of anemia in the third trimester of pregnancy with post-delivery ICU admission and preterm delivery.

Results: We found that MD is a rare event in Georgia; however, the maternal mortality ratio was notably higher than that in high-income countries. There was a higher proportion of direct causes of MD (62%) than indirect causes (38%), with hemorrhage and infections being the main direct and indirect causes, respectively. Moreover, SARS-CoV-2 infection within 30 days before delivery or during delivery was strongly associated with MD, post-delivery ICU admission, and CS. None of the individuals with confirmed SARS-CoV-2 infection during pregnancy had received coronavirus disease 2019 (COVID-19) vaccination. Additionally, 40.6% of pregnant women experienced anemia during pregnancy; however, there were only

rare cases of severe anemia during pregnancy in Georgia. Anemia during pregnancy was not significantly associated with post-delivery ICU admission; further, there were no increased odds of preterm delivery among pregnancies with anemia compared to pregnancies without anemia. Finally, 18.1% of pregnant women lacked valid hemoglobin (Hb) measurements in the GBR.

Conclusion: The initial findings of this thesis demonstrated the need to improve acute obstetric care in Georgia given that direct causes of death and hemorrhage were primarily linked to pregnancy complications and delivery. Further investigation revealed that the COVID-19 pandemic had negatively impacted maternal health in Georgia, with pregnant women infected within 30 days before or during delivery having significantly higher odds of MD and post-delivery ICU admission than non-infected pregnant women. These findings suggest the need to address possible gaps in perinatal health care; improve the quality of antenatal care (ANC); and ensure adequate management during delivery and the postpartum period in order to avoid sudden and rapid progression to severe conditions, which may increase the risk of adverse maternal outcomes. Few pregnant women, and none of the MDs, had received full COVID-19 vaccinations. Accordingly, given the confirmed effect of COVID-19 vaccination on disease severity, our findings suggest that national decision makers should implement strategies for improving COVID-19 vaccination among pregnant women. Additionally, stakeholders should pay attention to the high prevalence of anemia among pregnant women in Georgia, as well as among-region differences in the prevalence of anemia within Georgia. A significant proportion of women lacked valid Hb measurements in the GBR despite receiving state-funded ANC. Therefore, there is a need for concerted efforts to ensure precise and correct reporting of Hb measurements in the GBR during ANC visits.

DOCTORAL PROJECT IN SHORT

1 Scoping maternal care through the lens of maternal deaths: A retrospective analysis of maternal mortality in Georgia

Objective
To examine and classify maternal deaths in Georgia by direct and indirect causes of death.
Study Period
January 1, 2014 - December 31, 2017
Study Population
61 eligible maternal death cases, defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).
Exposure
Direct and indirect causes of death.
Outcome
Maternal death.

2 SARS-CoV-2 infection during pregnancy and the risk of adverse maternal outcomes in the Republic of Georgia: A national birth registry-based cohort study

Objective
To assess the odds of maternal deaths, post-delivery intensive case unit admission, and caesarian section in relation to SARS-CoV-2 infection during pregnancy among women who had attained a gestational age of ≥ 22 weeks at the time of delivery.
Study Period
February 28, 2020 - August 31, 2022
Study Population
All women registered in the Georgian birth registry and had attained gestational age week ≥ 22 at the time of delivery – 111,493 women.
Exposure
SARS-CoV-2 infections during pregnancy.
Outcome
Maternal death, post-delivery intensive care unit admission, and caesarian section.

3 Anemia during pregnancy and adverse maternal outcomes in Georgia: A birth registry based cohort study

Objective
To provide updated information about the national and regional prevalence of maternal anemia in Georgia and to evaluate the associations between anemia in the third trimester of pregnancy, maternal transfer to post-delivery intensive care unit, and preterm delivery.
Study Period
January 1, 2019 - August 31, 2022
Study Population
All women registered in the Georgian birth registry and had attained gestational age week ≥ 22 at the time of delivery, having at least one antenatal care visit during pregnancy and reliable hemoglobin measure registered in the registry – 129,959 women.
Exposure
Anemia at any time during pregnancy.
Outcome
Post-delivery intensive care unit admission and preterm delivery.

Designed using Canva

Source: https://www.canva.com/

4 Introduction

Maternal health is defined as the health of mothers during pregnancy, childbirth, and the postnatal period (3, 4). Maternal health indicators, alongside other indicators related to newborn and child health, are often used to describe a country's population health, quality of care, socioeconomic status, economic sustainability, and political priorities (6). Improved maternal health may be economically beneficial to the society and has positive effects with respect to gender equity, education, and poverty reduction (7, 8, 9). Accordingly, concerted efforts at the national level and international support to address challenges related to maternal, newborn, and child health are top priorities for global health. Globally, there has been broadening of the focus on women's health from just maternal health to a life-course approach that encompasses sexual, reproductive, and overall well-being (10). Given the increasing interest in maternal health, the global maternal mortality ratio (MMR) decreased by ≈35% from 339 per 100,000 live births in 2000 to 223 per 100,000 live births in 2020 (11). During the same period, Eastern Europe (Belarus, Russia, Ukraine, Moldova, Romania, countries from the Visegrád group, the Baltic states, the Balkans, and the Caucasus) achieved a significant reduction in MMR from 38 to 11 per 100,000 live births, representing a 71% reduction in the MMR (12, 13). Currently, ≈95% of all maternal deaths (MDs) occur in low- and middle-income countries (LMICs).

Alongside with MD, maternal morbidity such as heart disease and related problems, infections, and anemia are also concerns among health specialists. Notably, most MDs and severe maternal complications are preventable (12, 14). Despite global and specific regional reductions in the MMR, MDs and maternal morbidity remain high in LMICs. Relatively, maternal morbidity has been ignored and continues to be prevalent in LMICs (e.g., anemia) compared with in high-income countries (15, 16). Accordingly, maternal morbidity must be also prioritized to allow continued improved maternal health. However, several challenges in national healthcare systems, especially those related to the recent coronavirus disease 2019 (COVID-19) pandemic, humanitarian crisis, conflicts, and post-conflict settings have slowed global progress in the reduction of the burden of MDs and maternal morbidity as well as maternal health improvement.

4.1 MD and maternal morbidity

4.1.1 MD – definition and global incidence

MD is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy (1). MD and maternal mortality (MM) are often used synonymously. MMR refers to the number of pregnancy-related deaths within a given period divided by the number of live births during the same period, i.e., it is the incidence proportion of MD and often refers to the number of deaths per 100,000 population (1, 3). There are significant variations in the MMR worldwide. MDs are rare events and have been reduced to a minimum in high-income countries. Ireland, Luxemburg, Slovenia, and Lithuania had an MMR of 0, while Mexico, United States (U.S.), Turkey, and Norway reported MMRs of 54, 23.8, 13.1, and 3.7 per 100,000 live births, respectively, in 2020. The regions with the highest number of MDs are Sub-Saharan Africa and Southern Asia, which account for 70% and 16% of global MDs, respectively (17, 18).

4.1.2 Direct and indirect causes of MD

The 10th revision of the International Classification of Diseases categorizes (ICD-10) MDs into direct obstetric deaths (deaths resulting from the obstetric complications of pregnancy, interventions, omissions, incorrect treatment, or a chain of events resulting from any of the above) and indirect obstetric deaths (deaths resulting from a previously existing disease or diseases that developed during pregnancy and did not result from direct obstetric causes but were aggravated by the physiologic effects of pregnancy) (13, 19). Direct and indirect obstetric causes account for ≈75% and ≈25% of all MDs globally, respectively (12, 13, 20). Direct obstetric deaths include deaths due to postpartum hemorrhage (PPH), pre-eclampsia, hypertensive disorders, and pregnancy-related infections, while indirect obstetric deaths include deaths due to infections and non-communicable diseases such as malaria-related complications, anemia, and HIV (1, 21). There remains no benchmarking ratio for direct and indirect causes of MD given that the objective is to reduce the overall MM. However, in high-income countries, the proportion of indirect causes tends to be higher due to improved management of direct obstetric crisis; contrastingly, direct causes are more prevalent in LMICs, which could be attributed to limited access to quality obstetric care as well as lack of resources and infrastructure (22).

Globally, the leading direct cause of MD is PPH, which is defined as blood loss ≥500 ml within 24 h after birth (1), and it accounts for >20% of all MDs worldwide. Death caused by PPH is largely preventable and has been almost eliminated in high-income countries. However, the optimal methods of preventing, detecting, and treating PPH remain unclear. Further, there remain no standardized and effective interventions for PPH in LMICs (23). Taken together, despite PPH being the leading cause of MD, there have been insufficient global efforts for addressing it, which were further impeded by the COVID-pandemic (24). Other important direct causes of MD include pre-eclampsia and hypertensive disorders, sepsis, and unsafe abortion, which account for 14%, 11%, and 8% of all MDs, respectively (21).

4.1.1 MD reporting

Studies regarding maternal health require accurate quantification of MDs. The MMR can be directly calculated from data collected through vital registration systems, population-based surveys, or health services-related statistics. There remain significant challenges impeding

MMR estimation, including inaccurate registration of the numbers of MDs and births in most LMICs, problems with data quality, underreporting, data incompleteness, and misclassification of MDs. These challenges often result in underestimation of the MMR. Accordingly, MD-related estimates provided by the World Health Organization (WHO) and other international institutions are often adjusted in accordance with additional information received from each country (25, 26). However, since these are only estimates, caution should be applied when making between-country comparisons. Most LMICs have vital registration systems; however, given the lack of resources, these surveillance systems are unreliable, which impedes the accuracy of death reporting. Inaccurate reporting leads to misidentification of the causes of and risk factors for MD and maternal morbidity. WHO has proposed several solutions for addressing problems regarding data reporting and quality problems and ensuring accurate assessment of reported data. First, WHO has launched and leads the United Nations (UN) Maternal Mortality Estimation Interagency Group (MMEIG), which comprises WHO, United Nations International Children's Emergency Fund (UNICEF), United Nations Population Fund, and the World Bank. The UN MMEIG generates internationally comparable estimates of MDs to facilitate global monitoring. However, it is limited by the fact that the number of deaths is predicted rather than curated from reliable national surveillance systems. To mitigate this, WHO proposed a step-by-step evaluation of each case of MD using the Confidential Enquiry into Maternal Death (CEMD) approach. This is a systematic multi-disciplinary anonymous investigation of all MDs or a representative sample, which has improved MD reporting and prevention.

Taken together, ensuring consistent surveillance as well as precise and accurate generation of data and estimates may facilitate further improvements in maternal health (21).

4.2 Maternal morbidity

Maternal morbidity is defined as any health condition attributed to and/or aggravated by pregnancy and childbirth that negatively affect the woman’s well-being (2). Some women experience unexpected outcomes of labor and delivery that require intensive care unit (ICU) admission. ICU admission is defined as severe maternal morbidity that could lead to death (1, 2, 27, 28). In severe cases, severe maternal morbidity is termed as near-miss mortality, which is defined as a case where a woman nearly died but survived a life-threatening condition during pregnancy, childbirth, or within 42 days of termination of pregnancy (29). WHO has identified five conditions (PPH, severe preeclampsia, eclampsia, sepsis, and uterine rupture) and caesarean delivery associated complications that can serve as indicators for severe maternal morbidity (30).

This has provided a common global approach for monitoring and assessing maternal morbidity and mortality, and thus eventually facilitating their reduction (31). MDs are just the “tip of the iceberg” while maternal morbidity is the real base of the problem (5). Therefore, routine surveillance is warranted to track maternal morbidity in addition to MDs globally (31). The incidence rate of maternal morbidity is higher in LMICs than in high-income countries (2). Although decreasing maternal morbidity would lead to a decrease in MDs and severe maternal morbidity occurs at least 20 times more frequently than MD, there has been relatively scarce research on maternal morbidity compared with MM, especially in LMICs (31). Similar to MD, there have been challenges impeding accurate reporting of maternal morbidity in various countries and between-country comparisons. As aforementioned, these challenges are compounded by inaccurate data reporting resulting from the lack of a standardized data collection approach and inadequate health information systems (5).

4.2.1 Risk factors for MDs and maternal morbidity

Established risk factors for MD and morbidity include hemorrhage, eclampsia, or infection, with >80% of them being modifiable (12, 32, 33). Notably, some women may experience poor health or negative health outcomes without presenting any of the established risk factors (34). There are numerous and complex risk factors challenging maternal health, which also include direct and indirect causes of MD (12, 35).

Some risk factors, including eclampsia, are more prevalent in LMICs than in high-income countries, while others, such as embolisms, are equally prevalent worldwide (21). Moreover, other risk factors involve complications or comorbidities that develop during pregnancy or the postnatal period, including PPH (21, 36). Other conditions such as anemia may exist before pregnancy and worsen during pregnancy, especially without proper management (34).

The most common risk factors for adverse maternal outcomes include bleeding during pregnancy and PPH, delivery-related complications with chronic health effects, pre-eclampsia and eclampsia, unsafe abortion, infections, anemia, and heart disease. Women with these risk factors may experience high-risk pregnancies that warrant close and keen monitoring.

Sufficient capacity and competency within the healthcare sector as well as quality of care are crucial for decreasing the risk of MD and morbidity. Inadequate care during pregnancy increases the risk of adverse maternal outcomes (37). Quality care can facilitate favorable maternal health outcomes, even for high-risk pregnancies. Contrastingly, substandard, inadequate, or delayed care from health services may lead to adverse maternal outcomes, a situation referred to as “too little, too late” (38).

4.2.2 COVID-19 and its impact on maternal health

In 2020, the COVID-19 pandemic quickly spread worldwide. According to WHO-provided official statistics, there were >772 million individuals with COVID-19 and >6.9 million COVID-19 related deaths between March 2020 and December 2023 (39). Notably, estimates provided by WHO suggested that the actual number of fatalities exceeded the officially reported numbers by 2.75 times (40, 41). According to the UN, the COVID-19 pandemic slowed global economy growth by 3.4% in 2022. Accordingly, the number of people living below the extreme poverty level increased from 75 million to 95 million (42). There have been challenges in mitigating the global adverse effects of the COVID-19 pandemic impact. Previously, there was controversy regarding the effect of COVID-19 on maternal health and, in particular, pregnancy (43, 44). Subsequent studies have confirmed that pregnant women are at an increased risk of adverse maternal outcomes following SARS-CoV-2 infection (45, 46, 47). The COVID-19 pandemic has been shown to adversely affect maternal health in numerous countries through disruption of essential services or the direct adverse effects of COVID-19 on pregnancy (12). Notably, there was a significant worldwide reduction in the utilization of reproductive health services during the COVID-19 pandemic (48). Moreover, pregnant women are at an increased risk of severe illness following COVID-19 infection, which may be associated with negative maternal health outcomes. COVID-19-mediated inflammation in pregnancy may result in changes in the immune system, respiratory system, cardiovascular function, and coagulation, as well as a cytokine storm that can cause multisystem organ failure, which increases the disease severity and related morbidity and mortality (49). Notably, COVID-19 vaccination reduces the likelihood of MD and post-delivery ICU admission (50, 51, 52, 53). However, there remain no updated and reliable global numbers of infected pregnant women and their outcomes, which may facilitate evaluation of the impact of COVID-19 on MM and morbidity. There have been inconsistencies in the available reports, which may be attributed to significant among-country differences in healthcare sector performance, preparedness, and response. Additionally, there were among-study differences in case classifications and COVID-19 testing frequency (54).

4.2.3 Anemia in pregnant women

As aforementioned, anemia during pregnancy is an indirect obstetric cause of MD and morbidity; further, it is relatively more prevalent in LMICs (55). Anemia is defined as hemoglobin (Hb) level below 110 g/L.

According to WHO, the severity of anemia in pregnancy can be classified as mild (Hb level: 90–109 g/L), moderate (Hb level: 70–89 g/L), and severe anemia (Hb level: <70 g/L) (56). During pregnancy, there is a disproportionate increase in blood volume. Anemia is characterized by a decreased number of red blood cells and their Hb concentration, which renders the total oxygen-carrying capacity insufficient to meet the body's physiologic needs. Anemia during pregnancy involves disruption of red blood cell production, decreased Hb concentration in red blood cells, and decreased hematocrit values (57). The main causes of anemia are nutritional deficiencies (e.g., iron and vitamin B12 deficiencies); several infections; parasitic diseases; and heredity and genetic disorders affecting Hb production, synthesis, or survival (58). Other causative factors for anemia include poor balanced diet, insufficient protein intake, insufficient income, unhealthy lifestyle, behavioral and cultural aspects, and living at high-altitude environments (58). Anemia may involve significant problems with cessation of bleeding from a blood vessel, and thus increases the likelihood of PPH (59, 60). Specifically, increased anemia severity increases the likelihood of weakened uterine muscular strength, which contributes to PPH (61, 62). Moreover, anemia during pregnancy can adversely affect the immune system, which may increase the risk of maternal morbidity and mortality (63, 64) as well as infectious diseases (65). Notably, anemia during pregnancy exacerbates the COVID-19-mediated respiratory effects due to reduced oxygenation, which may lead to more severe respiratory symptoms, ICU admission, and the need for mechanical ventilation, due to the combined effects of pregnancy-related immune adaptations and anemia-induced immune weakness (66, 67). Accordingly, anemia during pregnancy increases the risk of preterm delivery, stillbirth, and low birth weight; further, anemia exerts a substantial economic burden (68, 69, 70, 71, 72). Even moderately severe anemia can cause adverse effects on maternal health (3). Moreover, anemia is associated with reduced productivity and worsened quality of life and can impose additional costs on society and families. Anemia substantially contributes to Disease-Adjusted Life Years among women aged 15–49 years and is a major contributor to >115,000 MDs annually, especially in Africa and Asia (10).

WHO's Global Nutrition Target seeks a 50% reduction in the prevalence of anemia among women of reproductive age (15–49 years) by 2030 (73) in order to meet the targets of Sustainable Development Goals (SDGs) 2 and 3, which involve improved nutrition, good health, and wellbeing (74). Notably, the COVID-19 pandemic has reduced attention towards anemia (75, 76).

4.3 Maternal health as a global health priority - from MDGs to SDGs

In 2000, UN member states declared their global commitment to the Millenium Development Goals (MDGs) by 2015, which included objectives to improve maternal health, including goal 5 "Improve maternal health" and target 5.A "Reduce the 1990 MMR by three quarters" (77, 78, 79, 80). The MDGs have been superseded by the SDGs, which were launched in 2015 with targets to be achieved by 2030 (79). In the SDGs, the indicator related to maternal health was as target 3.1 to reduce global MMR to <70.0 per 100,000 live births by 2030. The global MMR in 2020 was 223.0 per 100,000 live births; accordingly, concerted efforts are warranted to reach the target global MMR as follows:

- In countries with MMRs <420 per 100,000 live births in 2010, the MMR should be reduced by at least two thirds by 2030.

- In countries with a baseline MMR >420 per 100,000 live births in 2010, the rate of decline in MMR should be steeper so they can achieve an MMR ≤140 per 100,000 live births by 2030.
- In countries with a low baseline MMR in 2010, they should achieve equity in MMR for vulnerable populations at the subnational level.

Therefore, the global MMR should decrease by ≥6.4 % annually in order to achieve the target MMR (81). Accordingly, the targets regarding maternal health in the MDGs and SDGs are currently not being met. Between 2016 and 2020, the MMRs stagnated in 133 countries and substantially increased in 17 countries, mainly in western Europe, North America, Latin America, and the Caribbean (82). Thus, there is an urgent need for novel approaches for facilitating the meeting of relevant SDG targets (82, 83).

Among the relevant SDGs, target 2.2.3 seeks to eradicate all malnutrition types and halve the prevalence of anemia among women of reproductive age by 2030 (84, 85). A study conducted in 2022 indicated little progress in the reduction of the global prevalence of anemia, with an overall decrease from 41% to 36% among pregnant women globally between 2000 and 2019 (86).

Notably, several relevant goals and targets are reflected in the renewed UN Global Strategy for Women's, Children's, and Adolescents' Health 2016–2030 (87, 88).

4.3.1 Digital systems to accelerate progress towards the SDGs

As aforementioned, there have been challenges in terms of the accuracy and quality of data regarding MD and morbidity in numerous countries. WHO established a global multi-partner initiative to create strategies for Ending Preventable Maternal Mortality (EPMM) in 2015. This initiative sought to improve maternal health and contribute toward the achievement of the SDG target regarding MMR (14). The EPMM strategies clearly outline the importance of accurate MD counts, and thus the need to improve metrics, measurement systems, and data quality. This implies the implementation and maintenance of a complete civil registration

Figure 1. Ending preventable maternal mortality (EPMM): a renewed focus for improving maternal and newborn health and well-being

Source: World Health Organization, 2021

system, population registries, and accurate death and disease registration. Moreover, ten milestones were set in key areas (e.g., policy, quality of services, data, workforce, research, and others) for tracking the implementation of EPMM strategies (Figure 1). Some LMICs have a fragmented health system and services; further, they may provide poor-quality information that cannot be easily validated, which leads to errors. These countries often use paper-based data collection systems, which are often time and money resource intensive. Additionally, registry-related issues such as double entries, delays, impediments in data collection, and human errors leading to incomplete records, further limit data quality (3, 4). Notably, inappropriate and delayed recording as well as the lack of well-developed registration systems impede accurate reporting of MDs, especially in LMICs.

Registries should integrate into health systems in order to facilitate data pooling, promote continuity and quality of care, provide extensive data to inform research, collect comprehensive health-related information, facilitate the tracing of trace health trends, and reduce the reliance on expensive surveys and stand-alone data collection (89, 90). Technological advances have expanded the role of digital registries, which have offered more opportunities for scientific discovery, supported regulatory decisions, and informed health policy development and healthcare improvement.

4.4 Georgia in brief and the national healthcare system

Georgia – an upper-middle-income country in the Caucasus region – is located at the crossroads of Western Asia and Eastern Europe. It has an area of 70,000 km^2 that extends from the southern foothills of the Greater Caucasus Mountain range to the south-eastern shores of the Black Sea. It is bordered by Russia to the north, Turkey to the south-west, Armenia to the south, and Azerbaijan to the south-east (Figure 2). Its capital is Tbilisi. The country is divided into eleven regions; however, the Abkhazia and Tskhinvali regions are currently not under Georgia's de facto jurisdiction due to conflicts with Russian policy. Moreover, Russia’s involvement has impeded a defined constitutional status in Georgia's official territorial arrangement.

Figure 2. Map of Georgia.

Source: Mostphotos, https://www.mostphotos.com/en-us

Georgia has a population of 3,736,400, with 58.9% of this population living in urban areas (91). After the disintegration of the Soviet Union in 1991, there many challenges that impeded Georgia from regaining independence, with the most critical being the economic and social crises that affected the healthcare sector (92). This led to deep fragmentation of the national healthcare sector and disruption of all levels of service provision – starting from primary health care, including secondary and tertiary health services as well as public healthcare. Since 1994, Georgia's economy has improved following economic and political stabilization. From 1994 to 2022, the Gross Domestic Product (GDP) per capita increased from 519 $ to 6,672 $, with a steady real annual GDP growth from -10.4% in 2021 to 10.1% in 2022 (91, 93). Accordingly, Georgia moved from being a lower-middle to an upper-middle income country in 2015 based on the World Bank Atlas method. The country's healthcare sector has undergone several fundamental reforms, which have improved the population health status. These reforms mainly sought to ensure universal access to high-quality medical services, decrease fragmentation of the healthcare system, and decrease the financial burden attributable to high medical costs and increased expenditure on health. The country has embraced evidence-based medicine and implemented a health improvement programme for improving the quality of health care. Although public spending on healthcare remained relatively low compared with internationally recommended standards (93), there has been expanded healthcare coverage, which has considerably decreased out-of-pocket spending on healthcare services. Previously, public financing was fragmented between competing private insurance companies and various national programmes. However, since 2013, Georgia has implemented and expanded the Universal Healthcare Programme (UHC), which received public funding. Through this programme, every citizen is entitled to a basic package of healthcare services and demonstrates the country's commitment to the SDGs. Notably, most providers at all levels of the system are independent of government with respect to ownership and management. Moreover, the health system is dominated by private facilities, with ≈80% of the 17,949 available hospital beds being owned by private facilities (91, 94). In Georgia, there are 238 ANC centers and 12,158 obstetrics and gynecology beds have been registered (95). Moreover, there were 644 doctors and 603 nurses per 100,000 population in 2022, which is relatively low compared to other countries in the region (95, 96). Reforms implemented between 2008 and 2012 have supported the privatization of the national health system. The Ministry of Labour, Health and Social Affairs (MoH) prioritized strengthening the quality management system to ensure adequate and appropriate provision of quality healthcare services. Over the last 15 years, there have been several key factors regarding reforms in the country's health system, including health sector digitalization, collection of data regarding the utilization of services, collection of surveillance and epidemiological data, and establishment of registries. Implementation of integrated information technology systems within the health sector has been a priority for the MoH since 2012. Digitalization within other sectors have allowed advancements in the health sector; for example, implementation of a 11-digit personal identifier (ID) for Georgian citizens facilitated healthcare sector digitalization and supported interoperability among various registries (97, 98).

4.4.1 Georgian population health

The national healthcare strategy was updated in 2022 and continuous to focus on significant challenges within the Georgian public healthcare sector. Among the established priorities is communicable disease control. Georgia has achieved high coverage rates for routine childhood vaccinations (>90%); however, these have been disrupted by the COVID-19 pandemic. Notably, noncommunicable diseases are the leading causes of morbidity and mortality in Georgia, with cardio-vascular diseases accounting for 37% of them (95). Notably, excess mortality due to COVID-19 was at 82.0 per 100,000 population in 2021, which exceeded the WHO-provided mean estimate of 22.0 per 100,000 population for the European region (94). The average life expectancy in 2022 was 73.7 years. The infant mortality rate per 1,000 live births decreased from 23.0 to 7.6 (decrease by ≈65%) between 2000 and 2022, which is close to the WHO-provided mean estimate for the European region (7.5 per 1,000 live births in 2018) (more details are presented in Figure 3). The MMR in Georgia was 35.4 per 100,000 live births in 2022, which was almost two and a half times higher than the average for the WHO European Region (13.1 per 100,000 live births in 2017) (94, 95). Addressing the relatively high MMR has been a political priority for many years; accordingly, there have been studies on factors contributing to MDs in Georgia.

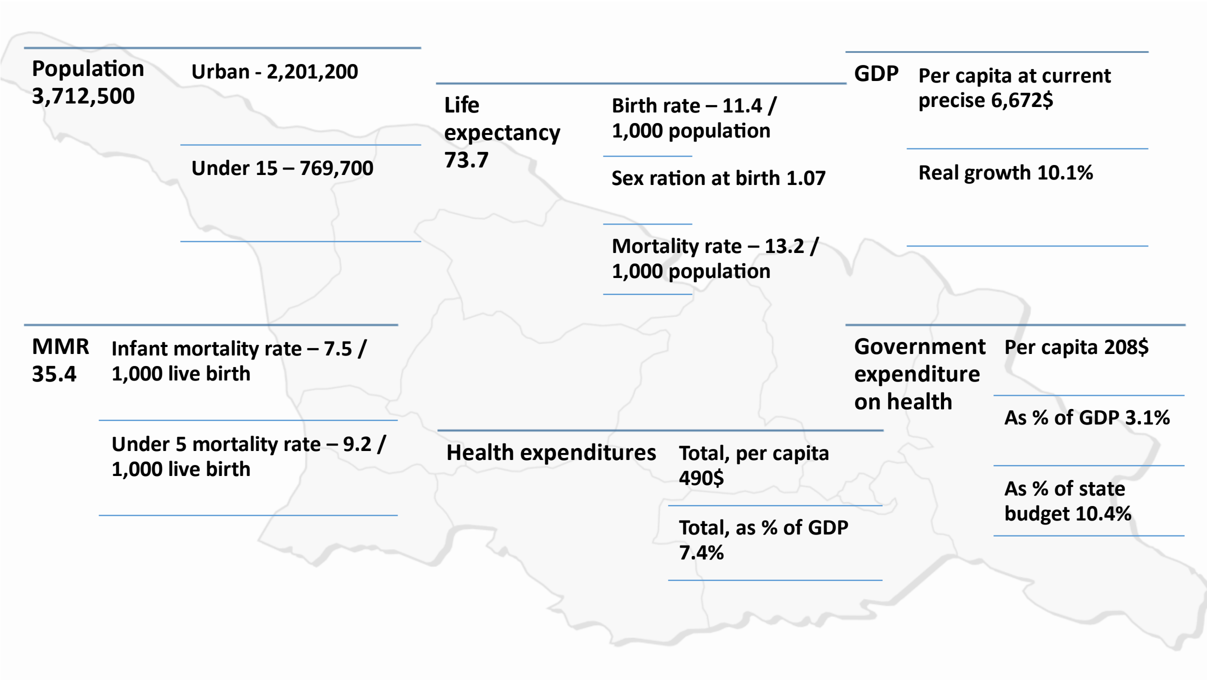

Figure 3. Demographic and socioeconomic characteristics, Georgia 2022

MMR, maternal mortality rate; GDP, gross domestic product.

4.4.2 Maternal health, MDG, and SDG progress in Georgia

Health is a fundamental human right in Georgia, with women and children being a priority. In 2000, as a signatory of the MDGs, Georgia began fulfilling its commitments to integrate goals within its national development strategies and has periodically reported their progress status. For example, perinatal services, including ANC, have been integrated into the UHC programme. In Georgia, the MMR was reduced by more than half from 49.2 per 100,000 live births in 2000 to 22.8 per 100,000 live births in 2012. Despite the significant 54% reduction in MMR, there remain challenges in the attainment of the target 5A (Georgian target for MMR was 12 per 100,000 live birth). From 2016 to 2020, the MMR fluctuated between 23.0 and 30.1 per 100,000. In 2021, the MMR increased to 71.8 per 100,000 live births, which could be attributed to the COVID-19 pandemic. The latest reported MMR was 35.4 per 100,000 live births in 2022 (94, 95).

Challenges in evaluated MDs involving underreporting and misclassification of deaths were documented by the Georgia Reproductive Age Mortality Study (RAMOS) conducted in 2008. According to RAMOS, the MMR was 44.4 per 100,000 live births in 2006, which differs from the officially reported value of 23.0 per 100,000 live births. Based on the RAMOS report, Georgia initiated significant steps to improve MD reporting and the capacity of national data analysis. For example, the country implemented a monetary penalty for failure to timely report a death event (98, 99, 100) in 2010. From 2012, Georgia adopted the WHO-recommended death registration reports form and classification, which includes the underlying cause of death; further, according to the new regulations, a medical death certificate should only be electronically issued (98, 99, 100). The National Statistics Office (GeoStat) began matching MD certificates to birth and fetal death certificates. In 2015, the National Center for Disease Control and Public Health (NCDC) introduced active surveillance of MDs, with the application of the electronic integrated disease surveillance system (EIDSS) and implementation of the verbal autopsy methodology for reviewing all pregnancy-related deaths (96). Notably, WHO recommends using the verbal autopsy technology to collect additional information regarding MD. Verbal autopsy was implemented to measure progress towards achieving SDG target 3 (14). Various international organizations and agencies have estimated the MM in Georgia, including the UN MMEIG and Institute for Health Metrics and Evaluation under the Washington University, with inconsistent reports. This inconsistency could be attributed to differences in the sources and reporting of figures, methodologies, and approaches in estimation (Details are shown in Figure 4).

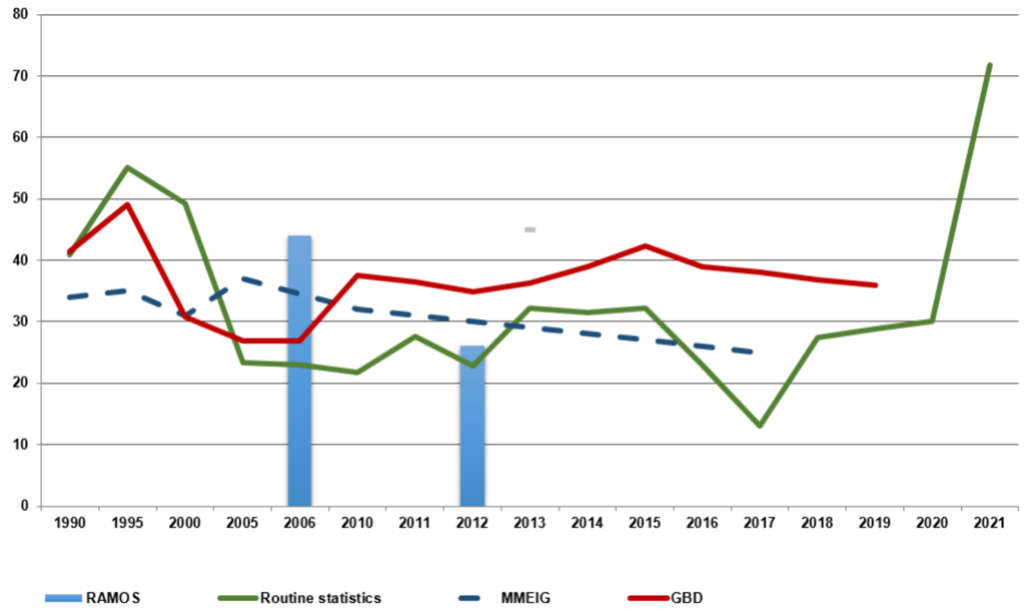

Figure 4. Maternal mortality according to the Reproductive Age Mortality Study (RAMOS), routine (official) statistics reported by the National Center for Disease Control and Public health of Georgia, Mortality Estimation Inter-Agency Group (MMEIG), and Global Burden of Disease (GBD) study from the Institute for Health Metrics and Evaluation, Georgia 2021.

Source: National center for disease control and public health, National Statistics Office of Georgia, 2022

The most recent national RAMOS, which was conducted in 2014, combined medical records with verbal autopsy diagnoses and detailed investigations of all MDs in Georgia between 2014 and 2015. This study demonstrated significant improvements in the death registration of women of reproductive age. Specifically, 98% of women of reproductive age were registered in Georgia's vital registration system in 2012, which higher than the corresponding value of 84% in 2006 (RAMOS 2008). Moreover, the level of underreporting of MDs in vital statistics were significantly reduced from 65% in 2006 to 39% in 2012; further, the MMR decreased from 44.4 to 26.3 per 100,000 live births. The findings demonstrated that improvements in the quality of care may have prevented 87% of MDs resulting from direct obstetric causes (25, 26, 93, 100).

In 2015, the Georgian government committed to accomplish the SDGs; accordingly, it has undertaken measures to adapt the 2030 Agenda to specific national circumstances (101, 102).

Similar to other countries, Georgia integrated SDGs into the state programs, with progress in the framework of “Health 2020” policy and their integration into reforms (102, 103). National authorities aim to reduce the MMR to 12 per 100,000 live births by 2030 in collaboration with specific international organizations; accordingly, they are implementing policies to improve perinatal health and are developing a reliable system for national surveillance, reporting, and registration (96, 100). Additionally, other state-funded maternal and child healthcare programs have been implemented to introduce ANC services as part of the UHC programme, which provide identification and management of high-risk pregnancies; screening of pregnant women for HIV, Hepatitis B and C, and syphilis; and free provision of folic acid and iron supplements to pregnant women (96, 99, 104, 105).

With support from the UNICEF, the MoH launched the regionalization of perinatal healthcare services in 2017, which seeks to grant I–III levels of care to maternity hospitals in Georgia in accordance with the predefined requirements for each level in terms of human resources, infrastructure, equipment, and laboratory and diagnostic services (96, 99, 100). This internationally recognized approach ensures that every maternity facility eventually meets the required standards. Moreover, an important WHO update on the provision of ANC in 2018 recommended an increase in the minimum number of visits from four to eight (94, 99). In 2022, at least 85.8% of pregnant women had at least one ANC visit and 99.7% of births were manned by skilled health personnel (95). Currently, postnatal care services have been integrated into the UHC programme.

According to the global SDG index measured in 2023, Georgia ranks 42th out of 166 countries (84, 95). However, Georgia remains to be on track in the reduction of MMR according to the SDG indicator 3.1, with challenges remaining in relatively low-quality antenatal, perinatal, and post-partum services (95, 101, 102). Similar to many other countries, the COVID-19 pandemic has hampered progress in Georgia towards achieving SDGs (106). Despite a rapid national pandemic response and making ANC services a top priority, there was an increase in MDs during the pandemic, which peaked in 2021 (71.8 per 100,000 live births). Furthermore, the caesarean section (CS) rate increased during the COVID-19 pandemic from 39.9% in 2019 to 44.3% in 2022, with 63.5% of these cases being elective CSs (95).

Another important aspect is the anemia prevalence among pregnant women in Georgia, which is addressed in SDG target 2.2.3. The National Nutrition Survey conducted by the NCDC and U.S. Centers for Disease Control and Prevention in 2009 sought to assess the prevalence of micronutrient deficiency in children and pregnant women based on data obtained from the national nutrition surveillance system. Here, the prevalence of micronutrient deficiency was 25.6% among pregnant women, which was substantially higher than those in high-income countries within the WHO European Region and North America (7%–14%) (107). This indicates that anemia is a public health concern among pregnant women; however, severe anemia is relatively rare (107, 108, 109). Despite the importance of achieving SDG target 2.2 and mitigating risk of anemia during pregnancy, the anemia prevalence in Georgia, its regional distributions, and its impact on maternal morbidity remain unclear. According to the national statistics, the prevalence of anemia among pregnant women increased from 10.6% in 2019 to 25.8% in 2022 (95).

4.4.3 Digital health registries related to maternal health in Georgia

Since the 2000's, there has been acute awareness of the limitations of the current health data-reporting systems in Georgia. Accordingly, national authorities and decision makers with support of international organizations implemented electronic reporting to the NCDC (from 2010) and urgent notification to the Maternal and Children's Health Coordinating Committee (MCHCC) under the MoH for any MD, stillbirth, or child death between the age of 0–5 years (from 2013) in order to improve medical care and data quality. The MCHCC is the body responsible for the national surveillance of maternal and child health. It ensures active tracking of reported MD cases and provides systematic multidisciplinary investigation of each death. Up to 2016, official data regarding MD and morbidity were manually collected from several sources in Georgia, including the GeoStat, MoH, and the NCDC. The Department of Medical Statistics under the NCDC collects mortality data from health facilities. Furthermore, several digital surveillance systems contain components related to reproductive health. For example, MDs are registered in the EIDSS, which facilitates retrospective tracking of MDs and severe complications. Additionally, the MCHCC receives notifications for the established CEMD audits. Notifications from medical facilities to the MCHCC are mandatory and should be performed within 24 hours, with all related medical papers being submitted within five days. However, given the extensiveness and complexity of health-related information, the national health sector has increasingly depended on information and communication technologies; thus, their integration is vital.

Despite offering a good case-tracing approach, paper-based data collection is time-consuming and complicated. MoH focused on enhancing reproductive health statistics, with a particular focus on timely reporting and accuracy. Accordingly, it prepared for the introduction of the new information system of maternal and child health management. Eventually, in 2016, the national Georgian Birth Registry (GBR) was established, which made Georgia one of the few middle-income countries that pioneered this national registry for maternal health surveillance (100, 110).

Currently, authorized medical facilities and bodies (including village doctors) report any MD to the vital registration system (VRS), with subsequent issuance of a death certificate (details presented in the Figure 5). Moreover, the GBR contains information regarding the deceased mother derived from the healthcare system.

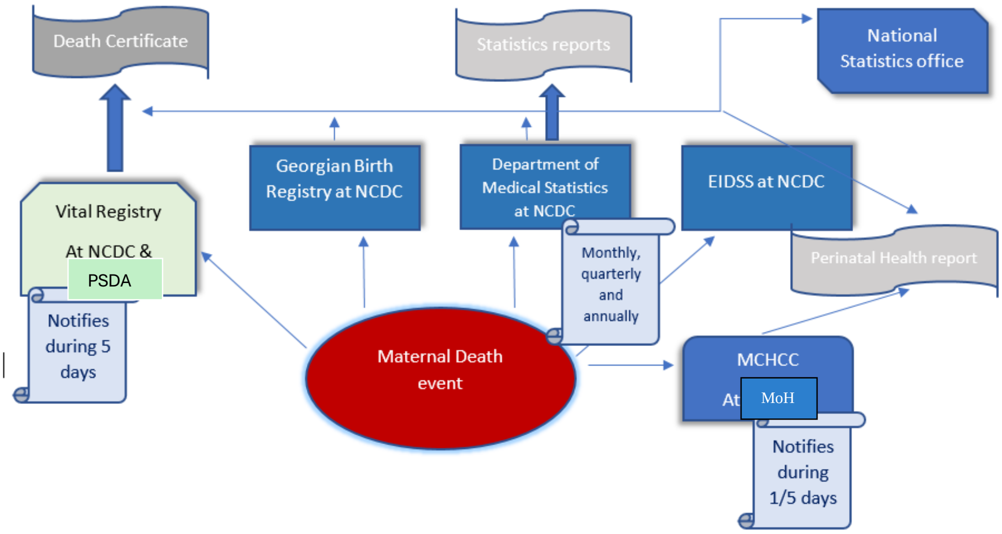

Figure 5. National system for maternal death reporting in Georgia.

NCDC, National Center for Disease Control and Public Health; PSDA, Public Service Development Agency; EIDSS, electronic integrated disease surveillance system; MoH, Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs

The GBR is a powerful tool for research on MD and maternal morbidity, which can inform significant advancements in health care. It facilitates proper data analysis (descriptive, comparative, trend analysis) to identify risk factors and patterns (correlation and causation, pattern recognition); develop and test interventions, and evaluate and refine improvements.

5 Research rationale

Improving maternal health, as well as reducing MD and maternal morbidity, are priorities among LMICs, including Georgia. To achieve SDGs related to maternal health and identify major challenges and gaps in the national health system, decision makers require evidence-based, accurate, and reliable statistics regarding MD and maternal morbidity. Specifically, information regarding direct and indirect causes of MDs as well as the quality of provided services are crucial to develop evidence-based interventions. For a long period, Georgia lacked precise, comprehensive, longitudinal, and individualized data regarding MDs and morbidity, with only aggregated data being available. Currently, Georgia has several high-quality national health registries; however, only few studies have analyzed data obtained from the national surveillance systems to address MDs and maternal morbidity.

6 Research aim

The overall aim of the thesis is to study MDs, maternal morbidity, and related risk factors using data from the GBR and other national digital health surveillance systems.

The specific objectives of this thesis were as follows:

1. To examine and classify MDs in Georgia according to direct and indirect causes of death (Paper I).

2. To assess the odds of MD, post-delivery ICU admission, and CS delivery with respect to SARS-CoV-2 infection during pregnancy among women at gestational week ≥22 weeks upon delivery (Paper II).

3. To provide updated information regarding the national and regional prevalence of maternal anemia in Georgia as well as to evaluate the associations of anemia during the third trimester of pregnancy with maternal admission to the post-delivery ICU and preterm delivery (Paper III).

7 Materials and methods

7.1.1 Data sources

In paper I, we used data obtained from several national health surveillance systems, including the GBR, VRS, EIDSS, and verbal autopsy reports. Additionally, we used reports from the CEMD and forensic services providers to assess direct and indirect causes of MD. In papers II and III, the GBR was the main source of data, along with the VRS and other digital registries (more information is described below), which were used for validation or extraction of additional data.

7.1.2 Case report forms for collecting data regarding MDs

Most information regarding MDs for paper I was obtained from data reported to the MCHCC, which receives death notifications within 24 hours. All MDs were cross-checked against the VRS. Crucial supplementary information was extracted from medical records and reports of verbal autopsy, forensic service reports, and EIDSS (described in section 7.1.2). For deaths registered after 2016, the GBR was an additional important data source. Information collected for each MD was transferred to a specially designed standardized case report form (CRF), and all diagnoses were filled in accordance with the ICD 10 classification system. The CRF summarized major information regarding each MD in terms of demographics, health, perinatal conditions, and other diagnoses in order to confirm the cascade of events leading to the MD.

7.1.3 Electronic Integrated Disease Surveillance System

The EIDSS was introduced in Georgia in 2004 under the One Health concept, which was developed by the respective U.S. agency. The system collects and distributes relevant data regarding notifiable diseases determined by the national law, ensures active surveillance and real-time follow-up, and facilitates secure interactions among the different levels of the national disease surveillance network. EIDSS can be accessed by all regional and district public health centers. From 2010, a special module for data collection and reporting of the deaths of women of reproductive age in Georgia were implemented in EIDSS, which has facilitated the countrywide review of pregnancy-related deaths.

7.1.4 The Vital Registration System

Paper I and Paper II employed the VRS to validate MDs. The VRS was launched in 2021 and is maintained by the NCDC in conjunction with the Public Service Development Agency under the Ministry of Justice. It registers data regarding all birth and deaths in Georgia and issues death and birth certificates. Medical certificates are created based on WHO recommendations, filled electronically, and automatically sent to the VRS. The notification should be received within five working days after birth or death (Joint order of the MoH and the Minister of Justice, №01-37/ n- №173 August 24, 2016, on approval of "Birth and death medical certificate details, forms, their completion and sending rules").

7.1.5 The Georgian Birth Registry

The GBR was launched following a long-lasting partnership between UiT the Arctic University of Norway, UNICEF Georgia, and the NCDC. It is the first national, digital birth registry created in a middle-income country.

The GBR provides an electronic platform that serves medical facilities and decisionmakers, keeps accurate statistical information for analytical purposes and research, and maintains surveillance of pregnancies and deliveries. After the necessary technical, administrative, and educational efforts, the GBR was officially launched on January 1st, 2016, encompassing all maternity units and ANC providers in Georgia (90, 110). Currently, the GBR digitally holds all birth-related data for all Georgian citizens. To promote the use of the GBR, clinics and hospitals do not receive government reimbursements for ANC and childbirth services unless the registry information is completed for each eligible woman. Compulsory nationwide medical birth registration for pregnant woman is initiated at the first visit to a medical facility, with data normally being collected between ≤13 weeks of pregnancy and end of pregnancy (latest 42 days after delivery). Representatives of the medical facilities are required to complete a standardized digital form within 24 hours after admission of pregnant or delivering women. The GBR contains >400 variables with several main components related to spontaneous abortions, pregnancy terminations, ANC visits, hospitalization, delivery-related information, and newborn-related data.

Additionally, the GBR contains information on maternal characteristics, medical history of previous and current pregnancies, birth-related conditions and complications if any, and information about the post-delivery period prior to discharge from the maternity home. Women are registered in the GBR through their aforementioned personal 11-digit ID number. All medical conditions are registered according to the ICD 10 classification system (1). The GBR has several mechanisms to reduce data-latency as well as prevent duplicated and erroneous data; additionally, it has some specific limitations for customized variables (e.g., age, weight, length, gestational age (GA).

The use of personal ID allows linkage of data from the GBR to other national registries. For example, during registration, a mother's identity (ID, date of birth) is verified and synchronized with the Population Registry, which is an information system maintained by the Ministry of Justice under the Service Development Agency that is used to identify a person and citizenship status. Moreover, GBR is regularly linked with the VRS. This allows validation of the number of births and deaths in the GBR against information provided by the VRS. The GBR is linked to the other digital health surveillance systems established by the NCDC, including the Immunization Electronic Module, Hepatitis' Screening Digital system, Cancer Registry, and the COVID-19 Laboratory Management System, to exchange important information and reflect services provided.

7.1.6 The COVID-19 Laboratory Management System

Paper II involved information extracted from the COVID-19 Laboratory Management System (LabCov registry). LabCov was launched in April 2020 and electronically records the results of SARS-CoV-2 diagnostic tests performed by private and state laboratories, throughout the country. Registration of tested people is performed immediately upon testing, with the test results being entered within 24 hours. Starting in June 2020, all pregnant women admitted to a birth center or hospital were routinely tested for SARS-CoV-2. From October 2021, routine testing of pregnant women during ANC visits was also implemented. The obligation to enter data is regulated by the Decree N01-26/N of 25 March 2019 of the MoH on the Procedure of Keeping and Providing Medical Statistical Information along with the amendment 01-43/N of 16 April 2020, which mandates data to be being uploaded within 24 hours after swab taking or testing (111, 112).

7.1.7 The Immunization Electronic Module

Paper II also used information from the Immunization Electronic Module, which registers all vaccinations performed countrywide. Starting from 2021, the registry was expanded, and information regarding COVID-19 vaccination was added. This registry was the primary source to obtain COVID-related vaccination status among pregnant women.

7.2 Study samples and variables

All three papers are surveillance system-based population studies; however, they differ in terms of study design and data collection approaches.

The study population for the entire doctoral project included pregnant women in Georgia from January 1st, 2014 to August 31th, 2022; however, different study years and samples were used for the respective three papers.

Paper I

In Paper I, which employed a case series design, we identified 84 MDs reported to the MCHCC between 2014 and 2017. We cross-validated each MD with information in the VRS using pregnancy-related ICD 10 codes. Eventually, we excluded 23 MDs cases, including 12 late MDs (occurring >42 days but <1 year after termination of pregnancy); nine accidental deaths; and two MDs that occurred in the occupied Georgian territories, and therefore lacked relevant information. Accordingly, 61 MD cases were included in the final sample. Information regarding demographics, health, and antenatal condition were extracted from medical records, GBR, VRS, EIDSS, verbal autopsy, and forensic service reports. The following variables were included: age, marital status, residency, parity, comorbidities, attendance to ANC, high-risk pregnancy, GA, and mode of delivery. Age was categorized in four groups: 18–24 years, 25–34 years, 35–47 years, unknown) while GA was categorized into five groups (preterm, 22–36 weeks; early term, 37–38 weeks; full term, 39–40 weeks; late term, 41–42 weeks; unknown). The mode of delivery was categorized into four groups (normal vaginal; planned CS; emergency CS; died during pregnancy). The time of death was categorized into five groups (death during pregnancy; during delivery; death within 24 hours after delivery; death within 2–6 days after delivery; death within 7–42 days after delivery).

Paper II

In Paper II, which was a registry-based retrospective cohort study, we explored the hypothesis that SARS-CoV-2 infection in pregnant women close to or at the time of delivery increased the odds of MD, post-delivery ICU admission, and CS delivery. We included 111,493 pregnant women, who were registered in the GBR, with GA ≥ 22 weeks at the time of delivery and delivered between February 28, 2020, and August 31, 2022. Data from the GBR was merged with information from the LabCov and immunization registries. The study population was classified into three exposure groups: no confirmed infection during pregnancy (reference group), confirmed infection from conception to >31 days before delivery (infection in early pregnancy), and confirmed infection within 30 days before delivery or at delivery. We included the following variables: age, education, residency, BMI at first ANC visit, parity, plurality, ANC visits, GA during first ANC visit, gestational diabetes, and COVID-vaccination status. Maternal age and GA during first ANC visit were used as continuous variables. Education was classified as primary, secondary, higher, or unknown. Residency was categorized as rural or urban. BMI at first ANC visit was classified as <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2. Additionally, parity was classified as primiparous or multiparous, while plurality was classified as singleton or multiple. ANC visits and gestational diabetes were dichotomized into yes or no. Additionally, complete COVID-19 vaccination was defined as receiving two vaccine doses in both women with confirmed infection (considered vaccination before SARS-CoV-2 infection) and those without confirmed infection (considered vaccination at any time during pregnancy).

Paper III

In Paper III, which was a registry-based retrospective cohort study, all data were extracted from the GBR. To examine the national and regional prevalence of anemia, we included women who gave birth between January 1, 2019, and August 31, 2022, and had a GA >22 weeks (n=166,043). We excluded individuals who did not attend any of the recommended ANC visits during pregnancy (n=7,375) and those without any data related to Hb testing (n=28,709). Accordingly, 129,959 women were included in the final study sample. All pregnant women were grouped according to the anemia severity based on WHO-recommended classification for anemia (56) and GBR data regarding the lowest measured Hb value in pregnancy: no anemia (Hb ≥110 g/L); mild anemia (Hb 100–109 g/L); moderate (Hb 70–99 g/L); severe (Hb <70 g/L) anemia. For women with repeated Hb tests registered in the GBR during their pregnancy, only the lowest measured Hb value was included. Additionally, we assessed the association between anemia in the third trimester and adverse maternal outcomes per severity groups, where moderate and severe anemia were combined into one group. Only women with at least one Hb measurement in the third trimester of pregnancy and a GA >28 weeks were included in the assessment of the association between anemia severity and adverse maternal outcomes, post-delivery ICU admission, and preterm delivery (n=105,811). In this study, the following variables were included: Hb, maternal age, residency, education, year of delivery, frequency of ANC visits, parity, plurality, mode of delivery, bleeding during pregnancy, BMI at the first ANC visit, GA at the lowest recorded Hb value, GA at delivery, and post-delivery ICU admission. Categorical variables were dichotomized as follows: parity (primiparous or multiparous), plurality (singleton or multiple), and bleeding during pregnancy (*yes* or *no*). Similar to Paper II, the number of ANC visits was divided into three groups (<4 visits; 4–8 visits; >8 visits). The mode of delivery classified as CS or vaginal delivery. BMI at the first ANC visit was divided into five groups (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–30 kg/m^2, >30 kg/m^2, and unknown).

7.3 Statistical analysis

All data handling and statistical analyses were performed using STATA (StataCorp LLC, College Station, TX, USA). STATA version 15 was used for Paper I, while STATA version 17 was used for Paper II and Paper III. In all three papers, nominal data are presented as frequencies and percentages. Continuous variables are presented as means and standard deviations.

Paper I

Paper I was a descriptive and exploratory study. For frequencies, confidence intervals (CI) were estimated as a Wald Interval to test the significance of independent variables and to evaluate standard errors. Information summarized in the CRFs were reviewed to assess the cascade of events leading to MD. First, we determined the final diagnosis of deceased women independent of the MCHCC decision, followed by classification of all MDs as direct or indirect causes of MD.

Paper II & III

For Paper II and Paper III, along with descriptive statistics, we estimated crude and adjusted odds ratios (ORs) between exposures (COVID-19 or anemia) and outcomes (MD, post-delivery ICU admission, and CS delivery for paper II or post-delivery ICU admission and preterm delivery for paper III) using binary logistic regression analysis. To identify possible confounding factors in the presumed causal pathways between exposures and outcomes, we plotted directed acyclic graphs (DAGs) using DAGitty.net. The assumed causal relationships depicted between the variables included in the DAGs are based on previous findings and underlying theory, as well as country-specific information.

In Paper II, models for MD were adjusted for age, education, BMI at first ANC visit, parity, gestational diabetes, and COVID-19 vaccination status. Models for post-delivery ICU admission were adjusted for age, BMI at first ANC visit, gestational diabetes, and COVID-19 vaccination status, Further, models for assessing the association with CS delivery were adjusted for age, education, BMI at first ANC visit, parity, and gestational diabetes. In the sensitivity analysis for post-delivery ICU admission, we excluded women with MD and CS delivery given that surgical intervention during delivery may result in maternal ICU admission and many MD cases are admitted to ICU prior to death. To ensure that the inclusion of women without recorded SARS-CoV-2 test results did not affect the results, we performed another sensitivity analysis, in which we restricted the models to women with recorded SARS-CoV-2 test results in LabCov during pregnancy.

In Paper III, we calculated the prevalence of anemia at any time during pregnancy among women who delivered at a GA >22 weeks. To assess the association between anemia and post-delivery ICU admission or preterm delivery, we combined the moderate and severe anemia groups given the low number of women in the severe anemia group. Based on the DAGs, the model for post-delivery ICU admission was adjusted for age, BMI, bleeding during pregnancy, CS delivery, and parity, while the model for preterm delivery was adjusted for age, education, BMI, bleeding during pregnancy, and plurality. All results were presented with 95% CIs. Moreover, to test for linear trend, continuous Hb values were included as an independent variable in the regression models and *P* for trend was assessed corresponding to one incremental change in Hb.

7.4 Ethical considerations

The doctoral project was revised and approved by the Institutional Review Board of the NCDC (IRB #2017-009). Given the extended period required for the PhD project, this Institutional Review Board renewed the approval (IRB #2023-001). UiT the Arctic University of Norway received anonymized data for Paper I. In 2017, when this project was initiated, these data were considered anonymous and did not fall under the Act of Medical and Health Research. During the PhD period, the Norwegian legislation has changed; accordingly, the Regional Committees for Medical and Health Research Ethics in Northern Norway has approved the studies (Reference: 577179). All included data were pseudo-anonymized before the researchers received the data.

Informed consent and data privacy

Registration in the national registries is mandatory according to Georgian law, and citizens cannot refuse registration; accordingly, there was no need to obtain consent from the study participants. A data protection impact assessment was developed by the Norwegian Agency for Services in Education and Research and approved by UiT the Arctic University of Norway, with the reference number 146252. The study reporting is consistent with the Helsinki declaration and the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline.

8 Results

8.1 Paper I

In Paper I, we aimed to classify MDs between 2014 and 2017 in Georgia by direct and indirect causes of death, using data from the national surveillance systems and in accordance with internationally approved criteria.

The MMR during the 4-year study period, including 26.7 per 100,000 live births in Georgia. Moreover, 44.3%, 77.0%, and 55.7% of MD cases were 25–34 years old, married, and lived in rural areas, respectively. Moreover, 49.9% of MD cases were multiparous, 52.5% had no pre-existing medical conditions, and 73.8% had low-risk pregnancies. Additionally, 62.3% of MD cases adhered to at least one ANC visit, 42.6% had preterm deliveries, and 52.5% underwent an emergency CS. Notably, 62.0% and 38.0% of MDs were due to direct and indirect obstetric causes, respectively. Among all direct causes of death (n=36), hemorrhage was the main cause in 18 MDs, which accounted for 29.5% (95% CI: 19.4–41.9) of all MDs. Additionally, 14 out of 18 MD cases with hemorrhage underwent CS and died from PPH. Extensive blood loss, which was indicated by a blood loss volume >1,500 ml, only occurred in 7 out of the 18 MD cases with hemorrhage. Hysterectomy was performed in 13 MD cases, with 9 of them presenting disseminated intravascular coagulation. Post-caesarean laparotomy was performed in five hemorrhage cases; however, none of these cases underwent uterine artery embolization as an alternative treatment. Pre-eclampsia was the dominant pregnancy-related disease associated with hemorrhage, which was mainly in combination with severe obesity and emergency CS. The leading indirect cause of MD was infection, which account for 45.5% of MDs with indirect causes and included leptospirosis, pneumonia, tuberculosis, meningitis, and hepatitis. Moreover, among the MDs indirect causes, three, three, and one were due to cardiovascular disease complications, suicide, and cholecystectomy-related complications during the postpartum period, respectively.

8.2 Paper II

Paper II aimed to assess the associations of SARS-CoV-2 infection during pregnancy with MD, post-delivery ICU admission, and CS delivery. Among the included patients (n=111,493), 12.4% had confirmed SARS-CoV-2 infection during early pregnancy, while 2.6% had confirmed infection within 30 days before delivery or at delivery. A total of 16,715 women had confirmed SARS-CoV-2 infection any time during pregnancy. Compared with pregnant women without confirmed SARS-CoV-2 infection during pregnancy, all those with confirmed SARS-CoV-2 infection in early pregnancy and SARS-CoV-2 infection within 30 days before delivery or during delivery were more likely to have higher education (37.8% and 34.2% vs. 31.6%, respectively), live in urban areas (80.0% and 74.9% vs. 72.8%, respectively), and have at least one ANC visit (97.7% and 97.1% vs. 95.4%, respectively); moreover, they were less likely to be non-vaccinated against COVID-19 (12.6% and 10.6% vs. 5.4%, respectively). However, the distribution of gestational diabetes was almost equal among all three study groups (0.2%, respectively).

Among all MDs (n=39), 59.0% had confirmed SARS-CoV-2 infection during pregnancy and none were fully vaccinated against COVID-19. Furthermore, among all women with a post-delivery ICU admission, only 5.7% were fully vaccinated against COVID-19.

The odds of MD were 43 times higher among women with confirmed SARS-CoV-2 infection within 30 days before delivery or during delivery compared to the reference group (adjusted odds ratio [aOR], 43.11; 95% CI, 21.99–84.55). Contrastingly, women with confirmed SARS-CoV-2 infection during early pregnancy did not have increased odds of MD compared to the reference group (aOR, 0.47; 95% CI, 0.06–3.59). The odds of post-delivery ICU admission were five times higher among women confirmed SARS-CoV-2 infection within 30 days before delivery or during delivery compared to the reference group (aOR, 5.20; 95% CI, 4.05–6.67). Contrarily, women with confirmed SARS-CoV-2 infection during early pregnancy did not have increased odds of post-delivery ICU admission compared with the reference group (aOR, 0.93; 95% CI, 0.71–1.21). Compared with the reference group, women with confirmed SARS-CoV-2 infection within 30 days before delivery or during delivery had 11% higher odds of CS delivery (aOR, 1.11; 95% CI, 1.03–1.20), while women with confirmed SARS-CoV-2 infection in early pregnancy experienced 7% higher odds of CS delivery (aOR, 1.07; 95% CI, 1.03–1.11). Analyses restricted to women with recorded test results in LabCov confirmed a strong association between SARS-CoV-2 infection and MD (aOR, 36.6; 95% CI, 16.6–80.7). Similarly, the associations between confirmed SARS-CoV-2 infection within 30 days before delivery or at delivery and post-delivery ICU admission (aOR, 4.80; 95% CI, 3.68–6.26) and CS delivery (aOR, 1.10; 95% CI, 1.01–1.19) remained significant.

8.3 Paper III

Paper III aimed to describe the prevalence of anemia during pregnancy in the different geographical regions in Georgia. Additionally, we assessed the associations between anemia during the third trimester of pregnancy, maternal post-delivery ICU admission, and preterm delivery. The prevalence of anemia during pregnancy was 40.6% during the study period (2019–2022). Mild, moderate, and severe anemia were present in 23.2%, 9.7%, and 0.4% of the study population, respectively. The prevalence of anemia differed across the 11 administrative regions in Georgia, with the prevalence being lowest in Samtskhe-Javakheti (25.1%) and Racha (34.4%) and highest in Adjara (47.0%) and Kvemo Kartli (46.5%). Notably, only 8.4% of pregnant women underwent Hb measurement before gestational week 13 and 8.1% did not undergo Hb measurement throughout their pregnancy despite making ANC visits. Additionally, there were substantial regional differences in the proportion of women without or with unreliable Hb measurements during pregnancy as well as the number of women without ANC visits.

Among 105,811 women with at least one Hb measurement during their third trimester, the mean maternal age of women diagnosed with any status of anemia was ≈28 years. Most of these women lived in urban areas, had secondary education, attended at least one ANC visit, had a normal BMI, had previously given birth, were pregnant with one fetus, and delivered vaginally. Notably, women with anemia were more likely to have more than eight ANC visits, have a BMI <18.5 at gestational week <13, and be multipara compared to women without anemia.

Women with anemia had higher odds of post-delivery ICU admission than the reference group (mild/moderate anemia: aOR, 1.19; 95% CI, 0.97–1.46; severe anemia: aOR, 1.24; 95% CI, 0.93–1.66). However, the *P* value for trend (0.13) indicated insufficient evidence for a linear trend and a non-significant relationship. Contrastingly, we observed a linear inverse association between anemia and preterm delivery (mild anemia: aOR, 0.95; 95% CI: 0.87–1.04; moderate/severe anemia: aOR, 0.93; 95% CI: 0.82–1.06, respectively, and *P* for trend = .01).

9 Discussion

The overall study objective was to perform a nationwide assessment of MD, maternal morbidity, and related factors using data obtained from national health surveillance systems. We found that MD is a rare event in Georgia; however, the MMR in our study was twice as high as that in high-income countries and far from the SDG MMR target of 12 per 100,000 live births (113). The proportion of direct causes of MD (62%) exceeded that of indirect causes (38%), suggesting suboptimal national obstetric care. Hemorrhage and infections were the leading direct and indirect causes of MD, respectively. Additionally, SARS-CoV-2 infection within 30 days before delivery or at delivery was an important risk factor for MD, post-delivery ICU admission, and CS delivery, demonstrating that the COVID-19 pandemic hampered progress in the improvement of maternal health in Georgia. Notably, 93.6% of pregnant women were not fully vaccinated against COVID-19. Regarding anemia in pregnancy, we found that severe anemia is a rare event in Georgia; however, ≈40.6% of pregnant women experienced anemia during pregnancy. Moreover, 20% of pregnant women lacked or had invalid Hb measurements, with substantial variances in regional reporting and the regional prevalence of anemia. There was no significant association between anemia during pregnancy and post-delivery ICU admission. Additionally, the odds for preterm delivery did not differ according to anemia status during pregnancy. However, our findings suggested a reduced quality of ANC services in certain geographical regions, and thus a need for interventions targeting these regions to improve the quality.

This is one from the first studies to use data from the GBR and other national digital surveillance systems to assess maternal health. Accordingly, it may inform strategic interventions for reducing and eventually eradicating preventable MDs, decreasing the burden of maternal morbidity, and accelerating progress toward SDG targets for maternal health.

9.1 MDs in Georgia

The average MMR between 2014 and 2017 was 26.7 per 100,000 live births, which consistent with official reports in Georgia over the last decade (96). Additionally, it is similar to MMRs reported in other middle-income countries for the same period, including 22.0 per 100,000 live births in China and Malaysia, 25.0 per 100,000 live births in Armenia, 27.0 per 100,000 live births in Azerbaijan, and 29.0 per 100,000 live births in Thailand (93). However, the MMR in our study was twice as high as than in most high-income countries. Notably, the number of MDs increased after the study period for Paper I (2014–2017); moreover, the MMR rose from 28.9 per 100,000 live births in 2019 to 71.8 per 100,000 live births in 2021 (95, 112, 113). According to the results from Paper II, the odds of MD in pregnant women with confirmed COVID-19 infections within 30 days before delivery or at delivery increased by 43 times, which may partly explain the increased MMR in Georgia during the pandemic. In this study, MDs in Georgia between 2014 and 2017 were classified according to direct and indirect obstetric causes, which helped elucidate the general and specific performance of the healthcare system as well as the quality of antenatal, perinatal, postpartum, and continuum of care. The latest global evidence shows a decrease and increase of MDs with direct and indirect causes, respectively, especially in high-income countries (20). This could be attributed to improved quality of perinatal services and improved management of direct causes of MDs (18, 114). In our study, direct causes accounted for 62% of MDs, which differs from the findings of RAMOS 2014, where 77% and 23% of MDs had direct and indirect causes, respectively. This inconsistency may be attributed to differences in the study periods and methodologies as well as data sources (routine health statistics and surveillance data from NCDC, hospital and ambulance service electronic datasets, regional death registers, community informants, personal interviews with the relatives of the deceased, and reviewing medical records at the last visited medical facility).

Notably, we found that hemorrhage and infections were the leading direct and indirect causes of MD, respectively (29.5% and 16.4%, respectively), despite them being preventable in settings with adequate resources and capacity to manage obstetric crises. Worldwide, hemorrhage is the leading cause of MDs, accounting for 27.1% of all MDs (20). Our findings are consistent with previous findings from 2016 on mortality causes in Georgia, where PPH was the most common direct cause of death, indicating limited progress in targeting this problem (24, 25, 96). PPH is a preventable cause of MD with several modern interventions, including proper diagnosis and management of anemia, early detection of PPH, active management during the third stage of labor, and artery embolization. However, our findings indicate that these interventions are not being applied given the missing corresponding information within the case-related medical documentations. Additionally, there was incomplete or missing information regarding the blood loss volume in the medical records and GBR, which could be useful for justifying or initiating customized treatment, including blood transfusion. The findings of Paper I made us aware about the absence of comprehensive assessment of anemia in Georgia despite evidence indicating that anemia can increase the risk of PPH (115). This led us to initiate another study. Accordingly, Paper III assessed the association between anemia during pregnancy and adverse maternal outcomes in Georgia. Notably, most MDs occurred in low-risk pregnancies without known severe pregnancy-related conditions, except for those undergoing emergency CS (the indication for CS was not available in the GBR and medical reports). Generally, there was no information regarding comorbidities in MD cases in the medical records and GBR; moreover, only few MDs occurred among women with high-risk pregnancies. Accordingly, the reason the patients underwent CS could not be determined. Importantly, unnecessary CS involves a risk of complications in both high- and low-risk pregnancies. Another key point is that infection was the leading indirect cause of MD. The most common causative infections were leptospirosis, pneumonia, tuberculosis, and meningitis. This was observed despite improvements in the provision of necessary services (e.g., antibiotic management, improved vaccination coverage, advancement in diagnostics, and improved access to laboratory services) for targeting infections over the last 30 years (94). Thus, there is a need to improve the availability and accessibility of more appropriate clinical solutions and comprehensive multidisciplinary approaches for managing infections.

9.2 The impact of SARS-CoV-2 infection on MDs and ICU admission

After consistent reduction in the Georgian MMR from 2000, it increased in 2019 (first pandemic year) and peaked in 2021 (71.8 per 100,000 live births) (95, 116). In the post-pandemic period, the MMR has re-stabilized and decreased to 35.4 per 100,000 live births in 2022 (95). Accordingly, pandemic and health emergencies reveal weak points in national healthcare systems and service provision. Delayed implementation of preventive measures and effective public health interventions during the COVID-19 pandemic significantly affected MDs in Georgia. Unfortunately, most LMICs lack post-pandemic data regarding the COVID-19 impact on maternal health, which impedes between-country comparisons (117). In our study, the odds of MD in pregnant women with confirmed COVID-19 infections within 30 days before delivery or at delivery increased by 43 times compared to the reference group, which is consistent with findings reported in other countries (93). Systematic reviews on the global impact of the COVID-19 pandemic indicated an increase in MDs in LMICs (118, 119, 120) but not in high-income countries (121, 122). This is expected since the availability of resources and capacity of healthcare sectors in high-income countries allows relatively rapid and effective responses during health emergencies.

Moreover, we observed an association between confirmed SARS-CoV-2 infection within 30 days before delivery or at delivery and post-delivery ICU admission. Our stratification according to the timing of SARS-CoV-2 infection was important since pregnant women with infections during early pregnancy lacked increased odds of MD or post-delivery ICU admission. Therefore, the timing of SARS-CoV-2 infection during pregnancy is a strong determinant of the maternal risk. Moreover, the increased odds of MD with SARS-CoV-2 infection can be physiologically explained by the virus triggering inflammation and a cascade of immune responses involving an increase in cytokines (49, 123). Altered immune responses trigger physiological changes in the cardiovascular and respiratory systems; moreover, COVID-19-related coagulation disorders during pregnancy increase the risk for adverse maternal outcomes (124, 125, 127).

In our study, a low proportion (6.4%) of pregnant women in Georgia had received full COVID-19 vaccination despite the established benefits of vaccination on COVID-19 severity during pregnancy (127, 128, 129). None of the MD cases with confirmed SARS-CoV-2 infection had been vaccinated. Moreover, only 5.7% of women with confirmed SARS-CoV-2 infections who were admitted to the post-delivery ICU were fully vaccinated. Promoting COVID-19 vaccination may further decrease the risk of adverse maternal outcomes and should be considered by national policy makers.

9.3 Anemia during pregnancy

Anemia during pregnancy has been associated with an increased risk of PPH, which can lead to post-delivery ICU admission (130). Paper I identified PPH as the leading direct cause of MD, which indicated poor management of PPH in Georgia. We sought to further elucidate the national and regional prevalence of anemia as well as the possible associations between anemia and adverse maternal outcomes. Pregnant women with PPH are likely to be admitted to the ICU. Therefore, given the lack of reliable information regarding blood loss, we used post-delivery ICU admission as a proxy variable in Paper III. However, mild or moderate /

severe anemia did not significantly increase the odds of post-delivery ICU admission (P for trend >.13 for both these associations); although, women with moderate / severe anemia had higher odds of ICU admission compared to the reference group.

Additionally, we observed that the prevalence of any-type and severe anemia during pregnancy was 40.6% and 0.5%, respectively. Since these women require treatment and follow-up during pregnancy, it is an important challenge to the national public health system. It is important to have accurate statistics regarding the anemia prevalence and regional distribution in Georgia to facilitate precise measurement of progress toward anemia reduction and mitigation. There were regional differences in ANC attendance and availability of Hb measurements, which affected the estimations of the regional prevalences of anemia. For example, in Kvemo Kartli and Samegrelo and Zemo Svaneti, which had the highest prevalence of anemia among the Georgian regions, ≥5% of the pregnant women lacked any ANC visits, which suggests that the true prevalence of anemia in these regions is unknown. Moreover, although Georgia has committed towards the SDG target 2.2 of reducing the anemia prevalence among pregnant women, 18.1% of all pregnant women with ANC visits lacked reliable Hb measurements during the whole pregnancy, with this proportion differing among regions. This suggests underreporting of anemia and points towards distortion of the true prevalence and distribution countrywide. Notably, the proportion of pregnant women with ANC visits without reliable Hb measurements was highest in Samegrelo and Zemo Svaneti, reaching 33.3%. It is important to identify factors impeding ANC visits and the reasons for regional disparities in reporting of Hb tests despite the state funding of the ANC programme. This could inform improvements in the quality and equity of the state-funded ANC programme. There are limited epidemiological studies on anemia status in the South Caucasus region, including Georgia. Therefore, we could only compare our results with the latest official numbers reported by the anemia sentinel surveillance sites between 2016 and

2017, which was further impeded by differences in the study design, samples, and methodologies. For example, the sentinel study was not countrywide, with information being collected from eight (health facilities) in only four Georgian regions (Adjara, Samegrelo, Tbilisi, Kakheti). Notably, the sentinel surveillance system applies a prearranged sample of sources that agreed to report all cases of one or more notifiable diseases (131). Additionally, it only included 1,203 pregnant women. According to this report, the prevalence of anemia among pregnant women was 7.4% (87), which is much lower that our observed value (40.6%). Contrastingly, the Global Nutrition Report 2020 indicated that the prevalence of anemia during pregnancy in Georgia was 28%, without a decrease within the last decade (132). This value differs from those reported by the sentinel surveillance study and our study. Moreover, according to the sentinel surveillance report, there were significant among-region differences in the anemia prevalence; however, the reported values were inconsistent with ours. Our findings indicated that the overall prevalence of anemia during pregnancy in Georgia is higher than the global estimate of the anemia prevalence among pregnant women (36.5%) and in neighboring countries such as Armenia (18.1%) and Azerbaijan (35%).

On the positive side, we observed no significant difference in the proportion of preterm deliveries according to the severity of anemia groups, with no increased odds of preterm delivery among women with any-type anemia compared to the reference group. This is inconsistent with reports from other low-income countries indicating that anemia during pregnancy increased the risk of preterm delivery (71, 72), but is consistent with reports from other middle-income countries (133, 134). Accordingly, this suggests that access to available resources is the main reason of this discrepancy and that the capacity of healthcare systems in middle-income countries facilitates proper responses to anemia as a public health threat.

10 Methodological considerations

10.1 Study designs

This PhD project applied two different observational study designs: case series and registry-based retrospective cohort study.

Paper I used a case series design, which per definition includes only exposed or unexposed potential cases or all cases with the same outcome (3, 131). A case series design focuses on the contextual analysis of several events or conditions and their relationships (131). We included all MDs from 2014 to 2017 based on its standard WHO definition (1). Therefore, in accordance with the case series design, we did not include control group. Since Paper I classify eligible MD cases according to direct and indirect causes, a case series was the preferred design for describing and quantifying MDs. Additionally, during the early stage of the PhD study, the objective was to conduct an exploratory analysis whose findings could inform hypotheses to be tested in more rigorous registry-based cohort studies in Paper II and Paper III.

Paper II and Paper III applied a registry-based retrospective cohort design to compare exposed (cases) and unexposed groups (controls). A registry-based retrospective cohort design has several advantages, including easy availability of data and being less resource intensive (time, cost, and effort in determining the number of participants). Moreover, since the GBR contains pregnancy-related and birth data for all Georgian citizens, the study sample size was large, which improved the generalizability of our findings at the national and even international level. This design is important for odds estimation, which facilitated our investigation of the effects of determined exposures on selected outcomes and elucidation of the strength of these association. This design had several weaknesses (e.g., missing data, coding variations across different registering facilities, lack of necessary information regarding confounding factors (131)); however, this is not necessarily attributable to the cohort design but rather the registration data.

10.2 Selection bias, information bias, and misclassification

All epidemiological studies involve errors. Bias refers to a systematic error leading to results or conclusions that are systematically deviating from the truth (3, 131). Two of the most common biases are *selection bias* and *information bias*.

Selection bias

Selection bias occurs when the study sample is not representative of the target population or due to poor sampling (4, 131). Paper II and Paper III used data obtained from the GBR, which includes data regarding >99% of all delivering women in Georgia (data from 2019). Since registration in the GBR is mandatory by law, the resulting nationally representative study population minimizes selection bias; however, some situations such as the lack of reporting or non-attendance for ANC services can result in selection bias.

To minimize selection bias in Paper I, all MD cases were included and independently reviewed and validated. Accordingly, we consider the risk of selection bias to be very low in this study. However, there remains a theoretical possibility of missing cases; for example, women who died while being unaware that they were pregnant. Therefore, these possible eligible for our study cases were not able to identify and include in analysis.

In Paper II, we only included women at gestational week ≥ 22 upon delivery and excluded those who died before gestational week 22. However, since we hypothesized that COVID-19 infection close to delivery increased the risk of adverse outcomes, only women who per definition had delivered were eligible for the study. In Georgia, very few women do not deliver in a hospital, which further reduces the risk of selection bias.

In Paper III, we excluded 7,375 (4%) pregnant women without ANC visits during pregnancy, which may have led to selection bias and affected our prevalence estimate. Although all these women had been registered in the GBR, they lacked ANC-related information such as Hb measurements. These women may have had poor health, which could have impacted our findings. Although we cannot determine the exact impact on our results, these women may have an increased risk of both anemia and adverse health outcomes.

Additionally, in Paper III, we excluded 28,709 women (18.1%) with no or unreliable Hb measurement during pregnancy from the logistic regression analyses. There were differences in education, number of ANC visits, and parity between women with and without Hb measurements. Accordingly, there may have been selection bias due to both ANC non-attendance and lack of Hb measurements / recording.

Information bias

Information bias arises from systematic differences in the collection, recall, recording, or handling of information (4, 131). In Paper I, we used paper-based medical records, which may contain errors. Moreover, data extraction could lead to information bias. It is possible that available data may have lacked crucial variables for our analysis. To minimize the risk of this systematic error, we used CRFs to precisely capture data for each included case. Each medical record and CRF was compared by medically trained persons; moreover, the forms were complemented with information from other data sources (e.g., GBR, EIDSS, verbal autopsy report) in case of incomplete medical records. This may have minimized information bias; however, we could not ascertain whether the information initially included in the medical records and other data sources was correct.

Registration errors in the GBR are a potential source of error in both Paper II and Paper III; however, such misreports may have been mainly random.

In Paper III, there was a substantial limitation regarding the lack of information regarding Hb measurements as aforementioned, which may be also considered as information bias.

Misclassification

Misclassification is an information bias arising from participants being assigned to an incorrect category (131). Both exposure and outcome can be misclassified, and the misclassification can be non-differential or differential (i.e., when there is equal or different probability of misclassification, respectively, in the exposed and control groups) (4, 131). Both non-differential and differential misclassification may lead to bias. Misclassification poses a certain limitation in our study. In Paper I, a potential source of misclassification bias was the lack of autopsy reports. All final diagnoses were validated using autopsy reports, if available. However, based on mainly traditions and cultural concerns, postmortem autopsy is rarely performed in Georgia. The absence of confirmation using autopsy reports impeded validation of the identified causes of MD, which may have led to misinterpretation of the cascade of events. Moreover, MD cases where both direct and indirect causes were reported in medical files were classified as having direct obstetric causes, which may have resulted in misclassification of results. Notably, two MD cases attributable to suicide were not classified as having direct obstetric causes of death. Although there was a renewed WHO-provided recommendation in 2012, it was not applicable in Georgia by the time of the study; accordingly, we followed the established national recommendation (135).

Moreover, misclassification should be considered in Paper II as well. From the start of the COVID-19 pandemic to the implementation of a routine testing strategy (implemented as mandatory testing for pregnant women from June 2020) during ANC visits in Georgia, a considerable proportion of women with undetected SARS-CoV-2 infection during early pregnancy may have been classified as non-infected women. Moreover, misclassification may have resulted from possible asymptomatic infection with COVID-19 between ANC visits, which was undetected and may have affected the composition of the reference and case groups. To address possible misclassification bias, we performed sensitivity analyses as aforementioned. In these sensitivity analyses, the identified associations remained strong; however, the effect estimates, especially for MD, were relatively weakened.

In Paper III, there was possible misclassification since ≈20% of eligible women with ANC visits lacked valid Hb measurements, which may have affected the prevalence estimation. There were significant challenges related to the lack of information regarding comorbidities in the GBR, which may have resulted in misclassification of sick women as healthy. Although comorbidities are rare, the lack of their registration may have resulted in residual confounding, which is further discussed below.

10.3 Confounding

Confounding is the error in the estimate of the measure of association between an exposure and outcome attributable to an alternative explanation. This may arise when another variable is associated with both the dependent and independent variables of interest. A confounding factor should not be on the causal pathway between exposure and outcome (131); accordingly, it is important to adjust for them in epidemiological studies to ensure valid inferences. Confounding is also a form a bias since it can distort the measure of association between an exposure and health outcome. There are some approaches for controlling confounding factors, including restriction and limitation of enrollment, matching confounders, and randomization. Unlike selection or information bias, confounding can be adjusted for after data collection using statistical models. In Paper II and Paper III, we adjusted for confounders in the regression analyses. Initially, we used DAGs to identify confounding factors in the presumed causal relationship between exposure and selected outcomes. DAGs are useful tool for graphically visualizing assumed causal relationships between variables: exposures, outcomes, and covariates (136). For both papers, the relationships depicted between the variables included in the DAGs were based on previous literature and the underlying theories. However, DAGs cannot specify the magnitude of relationship or describe its nature (linear or non-linear, positive or negative); moreover, they should include all plausible confounding variables. We attempted including all possible confounders in both Paper II and III; however, there remains a risk of residual confounding bias due to measurement errors within the observational study design. Additionally, the GBR contains limited information regarding women's socio-economic status, ethnicity, or behavioral preferences (i.e. smoking), as well as several comorbidities (e.g., kidney disease, infections, cancer, diabetes), which may have comprised potential confounders (137). In addition, the presence of undiagnosed health problems, may have resulted in residual confounding bias even after adjustment for the available confounders.

10.4 Missing and incomplete data

Missing and incomplete data is a challenge in epidemiological studies, especially those using newly established registries. Paper I applied paper-based medical records, with 31% of the MD cases having incomplete or missing information. To mitigate this problem, information for each MD was supplemented with information from other reliable sources provided by the NCDC, including the VRS, GBR, EIDSS, and verbal autopsy reports.

In Paper II and III, we used data from the GBR, which is a relatively new registry, and thus may contain some measurement errors. To minimize the risk for having a high frequency of missing data, the GBR has several protocols for improving data preciseness and quality. For example, prior to its implementation, several pre-determined limitations for ranges of certain variables were applied to avoid outliers or inconsistency (i.e., age, birth date, weight, length, GA). Moreover, regular validation of GBR is performed, including random and regular comparisons between GBR information and the respective medical records. Further, an internal quality control group was created in the Population Registry Unit within the Medical Statistics Department at the NCDC, which provides routine and ad hoc-based audit of the system.

Notably, our dataset for Paper II and Paper III contained missing data (i.e., comorbidities, gestational diabetes), which was addressed through the complete case analysis approach. Complete case analysis involves inclusion of only participants with complete data on the variables of interest. Thus, any cases with missing data were excluded from the regression analysis. This approach is straightforward and easy to apply. It has certain limitations, including loss of information or reduction of the sample size; however, other possibilities were not considered for Paper II and Paper III due to time constrains (e.g., multiple imputation).

10.5 Sample size

Large-scale studies may be inefficient and wasteful, while small studies may provide misleading or imprecise answers (131). Each of the three papers had different sample sizes. Paper I had a small study sample with a low absolute number of MDs. Accordingly, only 61 eligible MDs were included, and a larger sample size could not be obtained but since the aim of the study was to identify and classify MD in Georgia by direct and indirect causes of death from 2014 to 2017 and we included all possible cases, a larger sample size was not possible to obtain. For Paper II, the small sample size was also a challenge. Specifically, since MD is a rare event, only 39 deceased pregnant women were eligible for the study; moreover, with the number of MD cases in each exposure group being even smaller. This is reflected in the relatively wide CI for groups affected with SARS-CoV-2 infection during pregnancy. Therefore, even statistically significant results in our analysis should be interpreted with caution due to the small numbers of MDs. Additionally, given the small sample size and small number of vaccinations, we could not perform further sub-group analysis to assess the impact of COVID-19 vaccination within our study. In Paper III, given the small number of women with severe anemia, we combined women with moderate and severe anemia into one exposure group in order to improve the degree of precision in our estimation of the association between anemia and adverse maternal outcomes. However, this combination also led to loss of information since we could not determine the impact of severe anemia.

10.6 External validity

External validity, which is also defined as “truth beyond a study”, indicates whether the study conclusion can be generalized to different non-included populations with largely similar characteristics as the selected study population (138). Our findings seek to contribute to the global evidence regarding MD and maternal morbidity. All three papers within this project used data from the national health surveillance systems and GBR, which are nationally representative. Although our principal findings are not generalizable to other pregnant women outside of Georgia, they may be valid in countries with similar income levels and healthcare sector capacities. Additionally, the findings of Paper II are limited to countries that applied similar preventive measures and testing strategies for SARS-CoV-2 infection as Georgia. Notably, Paper II and Paper III only included women who had reached GA ≥22 and attended ANC visits. The results should be cautiously interpreted, and generalizability should be considered in a less explicit manner.

The results of Paper II indicate that full vaccination status is very rare. Therefore, the impact of SARS-CoV-2 infection on maternal health should only be generalized to non-vaccinated pregnant women populations within settings similar to those in Georgia.

11 Conclusion

This thesis demonstrates that direct obstetric causes are the most common among MDs in Georgia, mainly due to obstetric complications from interventions or from a chain of events during pregnancy, labor, or the postpartum period. Hemorrhage was the most common direct cause of death. Taken together, these findings indicate that in order to reduce pregnancy-related negative outcomes and obtain similar proportion of direct vs. indirect causes of MDs as those in high-income countries, interventions for care during pregnancy, labor, and delivery should be tailored to improve management of the most common causes of MDs in Georgia, including hemorrhage. Additionally, we found that infections were the leading indirect cause of MDs. Consistent with this finding, the COVID-19 pandemic was found to adversely affect maternal health in Georgia since women with infections close to or during delivery had considerably increased odds of MD and post-delivery ICU admission. COVID-19 vaccination was rare; therefore, there is a need to further promote vaccination among pregnant women in Georgia. Further efforts to identify possible gaps in perinatal and obstetric care and treatment of women during pregnancy and delivery are also warranted.

The low prevalence of severe anemia among pregnant women in Georgia is good for the national healthcare sector. Contrastingly, the high prevalence of mild and moderate anemia during pregnancy, large regional differences in the prevalence of anemia during pregnancy, and the lack of valid Hb measurements in ≈20% of pregnant women represent challenges in Georgian healthcare. Moreover, systematic scientific research is essential to develop strategies that effectively address causes of both MD and morbidity.

Nonetheless, our findings can generally inform maternal health stakeholders to scale up progress toward SDGs related to maternal health in Georgia.

12 Implications and recommendations

This PhD project identified several challenges related to the required quality of national reproductive health and ANC services in Georgia. Specifically, the findings of this thesis indicate the following:

i) Direct causes of MD are more common than indirect causes, and this proportion is strongly associated with the quality of antenatal, perinatal, postpartum, and continuum of care. Interventions should be tailored toward enhancing emergency obstetric care, training and capacity improvement for healthcare workforce, and improving healthcare resource availability and infrastructure. Moreover, there was a notably high proportion of low-risk pregnancies among MD cases, as well as low proportion of comorbidities among all pregnancies registered in the GBR. Therefore, it is important to enhance optimal obstetric care as well as monitoring and modernization of ANC guidelines for timely detection of high-risk pregnancies and comorbidities. These will guarantee improved management of pregnancies and mitigation of obstetric emergencies. Eventually, these measures could decrease the proportion of MDs due to direct obstetric causes, decrease the MMR, and eliminate preventable MDs. Additional, establishment of routine autopsies for all MD cases may help determine the leading cause of death and elucidate the real chain of event;

ii) There is sub-optimal care for PPH due to lack of access to multidisciplinary interventions and the application of checklist-based protocols for the timely management. Regarding blood transfusion interventions, there were missing data regarding the blood loss volume and other justifications for the initiated treatment. Further improvement of maternal health outcomes across Georgia requires consistent support to the medical personnel and enhancement of their capacity with modern knowledge and skills to manage life-threatening conditions. Continued regionalization of maternity facilities, their selected contracting, and integration with multi-profiling medical centers will further facilitate capacity development and quality improvement of provided services. Our findings demonstrate the need for additional training of the health workforce, including obstetricians, physicians working in maternity wards, and midwives, as well as re-establishment of Continuous Medical Education / Development to tackle the knowledge gap;

iii) During our research period, a low proportion of pregnant women were fully vaccinated against SARS-CoV-2 infection. Since we found that SARS-CoV-2 infection close to delivery adversely affected maternal health, it is important to intensify efforts to promote vaccination of reproductive-aged and pregnant women;

iv) Although anemia is a priority and target for SDGs, it continuous to pose a national public health challenge; moreover, there is a high proportion of missing and unreliable Hb measurements in GBR. Accordingly, there is a need for an even stronger public health response and policy implementation toward utilization of public health services, revision of registration structure of service-related information in the GBR, identification of factors responsible for the lack of Hb measurements, and revised strategies to ensure that women in Georgia have equal access and receive optimal care independent of their place of residence;

v) There is limited evidence regarding maternal morbidity and near-miss cases in Georgia. It is advisable to initiate a systematic approach that facilitates feasible tracking, follow-up and evaluation of severe maternal morbidity among pregnant women. Moreover, it is recommended to expand the GBR capacity and minimum follow-up period to 40 days in order to increase the total post-partum period coverage;

vi) Finally, since our findings contribute toward the available evidence regarding SARS-CoV-2 infection during pregnancy and its impact on maternal health, our findings could inform public health stakeholders regarding strategies suitable for targeted mitigation measures for most vulnerable groups and preparation of a national healthcare system that can have better responses to other possible outbreaks.

13 Future perspectives

Our findings indicate the need for comprehensive, in-depth future studies on specific issues, including a quality study on the skills and competencies of medical personnel as well as precise analysis of quality of care at any level of the reproductive health system.

CS generally has intrinsic risks and involves a cascade of complications. The high proportion of CS relative to vaginal deliveries among low-risk pregnancies demonstrates the need for future studies on the reasons underlying CS rates in Georgia.

Moreover, there is a need for future studies evaluating SARS-CoV-2 infection at pre-conception and various pregnancy trimesters and its impact on pregnancy and perinatal outcomes. Specifically, clinical audits of all MDs, supported with in-depth research to determine the cascade of events, identify the direct and indirect causes of death, and elucidate their association to SARS-CoV-2 infection, may inform interventions for improving care of SARS-CoV-2 infected women. Additionally, to enhance public health response, continued research on infected pregnant women according to SARS-CoV-2 vaccination status, timing of vaccination, and vaccine types with proper follow-up time is warranted. These studies can increase population awareness about vaccination as an important public health intervention against infections.

Finally, we analyzed anemia among pregnant women and adverse maternal outcomes. Further studies considering different types of anemia and possible treatments received are warranted. Moreover, it is important to conduct qualitative studies for identifying the reasons underlying the high proportion of GBR-registered pregnant women without ANC visits as well as those with ANC visits but without reliable Hb measurements.

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Paper I

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Scoping maternal care through the lens of maternal deaths: A retrospective analysis of maternal mortality in Georgia

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ABSTRACT

Introduction: Reduction of the maternal mortality ratio (MMR) to 12 per 100,000 live births by 2030 is a priority target in Georgia. This study aims to assess and classify MM in Georgia by direct and indirect causes of death from 2014 to 2017, using data from the national surveillance system and in accordance with internationally approved criteria.
Material and methods: In this secondary study, MM data was retrieved from the Maternal and Children's Health Coordinating Committee and validated with data from the Vital Registry System and the Georgian Birth Registry. The study sample comprised 61 eligible MM cases. Relevant information was transferred to case-report forms to review and classify MM cases by direct and indirect causes of maternal death.
Results: The MMR during the study period was 26.7 per 100,000 live births. The proportion of direct causes of maternal death exceeded that of indirect causes, at 62% and 38%, respectively. The leading direct cause of maternal death was haemorrhage, while infection was the most frequent indirect cause. 52.5% of MM cases had no pre-existing medical condition, 62.3% had frequent adherence to antenatal care, and 52.5% had emergency caesarean sections.
Conclusion: In Georgia, direct causes of maternal death exceed indirect causes in MM cases, with haemorrhage and infections, respectively, being most common. These findings are important to ensure optimal and continuous care and to accelerate progress in the reduction of MM in the country.

Introduction

Maternal mortality ratio (MMR) is an important indicator of maternal health and perinatal care. Although significant progress has been made in the past decade [1–2], the global reduction of MMR remains a critical challenge. Following the United Nation's Millennium Development Goals by 2015, maternal health was also prioritised in the Sustainable Development Goals, with the target to reduce MMR below 70 per 100,000 livebirths by 2030 [2–3]. Recent studies of maternal mortality (MM) have demonstrated that 94% of all maternal deaths occur in the developing world [4]. According to the WHO, the MMR in low-income countries was 239 per 100,000 live births compared to 12 in the rest of the world in 2015 [5–8]. Direct obstetric causes account for about 86% of all maternal deaths globally, with haemorrhage being the most common cause [7]. However, most MM cases are preventable, and about 50% of cases are avoidable [9,10]. In order to reach the desired reduction in MMR, efforts must focus on the improvement of all parts of the continuum of reproductive healthcare, accurate surveillance, and understanding the causes of maternal death [2,9,10].

Over the last decade, Georgia, a developing lower-middle-income

Abbreviations: MM, maternal mortality; MMR, maternal mortality ratio; WHO, World Health Organisation; ANC, antenatal care; MCHCC, Maternal and Children's Health Coordinating Committee; MoH, Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs of Georgia; NCDC, National Center for Disease Control and Public Health; VRS, Vital Registry System; GBR, Georgian Birth Registry; ICD-10, International Classification of Diseases, 10th revision; CI, confidence interval.

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country with a population of 3,719,300 [11], has embraced evidence-based medicine and implemented a health improvement programme with the aim of bettering the quality of health care. State expenses for healthcare increased 2.5 times since 2012, and these expenses currently claim 3.7% of the country's gross domestic product. In 2013, Georgia launched its Universal Health Care Programme, which entitles every citizen to a basic package of health services and is a visible demonstration of the country's commitment to the Sustainable Development Goals. Perinatal services are integrated into this programme, including antenatal care (ANC). According to official statistics, from 2006 to 2016, the MMR fluctuated between 32.1 and 23 per 100,000 live births [11,12,13]. The health improvement programme also sought to implement relevant policy to improve perinatal health and develop national surveillance, reporting, and registration systems and to reduce the MMR to 12 per 100,000 live births by 2030 [13,14].

The Maternal and Children's Health Coordinating Committee (MCHCC), part of the Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health, and Social Affairs of Georgia (MoH), receives notification of each maternal death within 24 h of its occurrence. Reporting of all medical information related to these maternal deaths is also mandatory. The MCHCC is responsible for a national surveillance and response system based on Confidential Enquiries into Maternal Deaths. This entails active tracking and systematic multidisciplinary investigation of all maternal deaths occurring in Georgia, followed by a response that aims to avoid future maternal deaths and improve maternal health care [15,16,17]. In 2012, Georgia implemented the WHO case-report form for death registration and classification. In addition, under the administration of the National Centre for Disease Control and Public Health (NCDC), the country created the Georgian Birth Registry (GBR), enhanced Vital Registry System (VRS), improved follow-up of maternal deaths through the Electronic Integrated Disease Surveillance System, and implemented the verbal autopsy methodology as part of the surveillance of MM. Moreover, specific guidelines, clinical protocols, and tailored courses for the management of common causes of maternal death were created and provided to medical personnel. Details of the surveillance of MM introduced by the MoH and the reporting and registration supported by the NCDC are described elsewhere [13,18].

So far, little attention has been given to surveillance system-based studies. There are few studies that scrutinise persistent causes of MM in developing countries like Georgia, where there are a shortage of appropriate epidemiological reports based on reliable data. No study has yet employed data from the Georgian surveillance system to evaluate whether this data can be used by stakeholders to direct efforts to improve maternal healthcare and thus accelerate progress toward the reduction of MMR in Georgia. Therefore, this study aims is to assess and classify MM in Georgia by direct and indirect causes of death from 2014 to 2017, using data from the national surveillance system and in accordance with internationally approved criteria.

Materials and methods

We defined maternal death according the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), i.e., the death of a woman while pregnant or within 42 days of delivery or termination of pregnancy through any causes associated with, or exacerbated by, pregnancy or its management; it did not include deaths from incidental or accidental causes [19].

This study utilised secondary data provided by the MCHCC. All MM cases reported to the MCHCC for the years 2014 through 2017 were collected, reviewed, and validated by the study authors during 2018. The final study sample comprised 61 eligible MM cases, which were registered officially in Georgia as MM cases during the same time period.

Causes of maternal death were classified as direct (obstetric complications of the pregnant state or its management) or indirect (resulting from a previous existing disease or a disease that developed during pregnancy, and which were not due to a direct obstetric cause), and categorised by ICD-10 code [19]. If both direct and indirect causes of death were recorded, and the starting mechanism for the chain of events was determined to be obstetric, the case was classified as having a direct cause of maternal death. Suicide (n = 2) was not included as a direct cause of death in this analysis, contrary to the recommended practice of the ICD-MM [20]. Indeed, ICD-MM recommended practice is not yet accepted worldwide, and Georgia currently follows ICD-10 classifications. Therefore, suicide was defined as an indirect cause of maternal death, following the ICD-10 classification of this term, excluding mental and behavioural disorders associated with the puerperium from direct cause of death. Final diagnoses were validated with autopsy records when available.

Relevant information from MCHCC medical documents was transferred to a standardised case-report form, which was designed for this particular study. The form synthesised data on demographic characteristics, health, perinatal conditions, and other diagnoses (recorded by ICD-10 code) in order to fully ascertain the cascade of events leading to maternal death and establish diagnoses independent of the MCHCC decision. In MM cases with insufficient information in the MCHCC, VRS, and GBR, demographic or obstetric data were acquired from additional NCDC sources (Electronic Integrated Disease Surveillance System; verbal autopsy).

The MMR for the study period was defined as the number of eligible MM cases per 100,000 live births. The confidence interval (CI) was estimated as a Wald Interval. All analyses were performed using STATA 15 (StataCorp LLC, College Station, TX, USA). In analyses of direct and indirect causes of maternal death, MM cases that occurred outside of medical facilities with no autopsy or verbal autopsy could not be classified and were excluded.

Ethical consideration

The Institutional Review Board of NCDC approved the legal aspects of the study (IRB #2017-009). In addition, regional Committees for Medical and Health Research Ethics (REC North) approved the protocol (Ref: 2017/404/REK nord). Personal identification remained hidden to the investigator at all times and the data are free from personal identifiers.

Results

Over the 4-year study period (2014–2017), there were 228,300 live births in Georgia [11] with an MMR of 26.7 per 100,000 live births. All MM cases reported to the MCHCC during the study period (n = 84) were identified (including incidental, accidental, and late maternal deaths), reviewed, and validated against MM cases in the GBR and VRS using the unique personal identification number assigned to Georgian residents/citizens. Pregnancy-related ICD-10 codes (O00-O95 and 98-99, A34, B20-B24, C58, X60-X84) were used for additional validation of MM cases or identification of possible misclassified MM cases in both registries [19], but this process did not reveal any additional MM cases for this period in Georgia. Following the maternal death definition in the ICD-10, and after validation in the VRS and GBR, 23 MM cases were excluded by the study authors (12 due to late maternal death, 9 due to accidental death, and 2 due to occurrence in occupied territories in Georgia with lack of information). Thus, 61 eligible MM cases comprised the study sample (Table 1). The majority of MM cases were 25–34 years old (44.3%), married (77%), and lived in rural areas (55.7%). Medical facilities could not be classified by the level of provided services (primary, secondary, and tertiary) during the study period, as this classification was only completed after 2017 in Georgia. A large proportion of MM cases were multiparous (49.9%), had no pre-existing medical conditions (52.5%), and had low-risk pregnancies (73.8%). Moreover, 62.3% of MM cases adhered to obligatory ANC, 42.6% had preterm deliveries (between 22 and 36 weeks of gestation), and 52.5% had an

Table 1
Selection of maternal mortality cases. Georgia, 2014–2017.

	2014	2015	2016	2017	Total
Total cases	26	24	17	17	84
Excluded cases					
Late maternal death	5	3	1	3	
Accidental death	–	1	4	4	
De facto territories	–	–	1	1	
Final study sample	21	20	11	9	61

emergency caesarean section (CS) (Table 2).

Thirty-six (62%) MM cases were due to direct causes of maternal death, and 22 were due to indirect causes (38%). Three MM cases were unclassifiable, as the death occurred outside medical facilities with limited medical data. Due to this issue, these cases were excluded from the further analysis. Two of the unclassifiable cases died during pregnancy, and one in the late postpartum period. When considering direct causes of maternal death, three MM cases (8.3%) died from anaesthetic complications, two during childbirth, and one 7–42 days postpartum after oesophageal haemorrhage and sepsis caused by a misplaced tube during intubation. Two deaths (5.5%) were related to ectopic pregnancies, three to amniotic fluid embolism (8%), and six to venous thromboses (18%). Four MM cases (11.1%) were attributed to eclampsia and the haemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome (Table 3).

Table 2
Demographic and prenatal characteristics associated with maternal mortality. Georgia, 2014–2017.

	Total n = 61 n (%)
Age groups	
18–24	14 (22.9)
25–34	27 (44.3)
35–47	19 (31.2)
Unknown[b]	1 (1.6)
Marital status	
Married	47 (77)
Never married	9 (14.75)
Unknown	5 (8.25)
Parity	
Primiparous	27 (44.3)
Multiparous	30 (49.4)
Missing[c]	4 (6.6)
Residency	
Rural	34 (55.7)
Urban	27 (44.3)
Pre-existing medical condition	
Yes	15 (24.6)
No	32 (52.5)
Unknown	14 (22.9)
Adherence to antenatal care	
No care	6 (9.8)
1–4	28 (45.9)
>4	10 (16.4)
Missing	17 (27.9)
High-risk pregnancy	
Yes	16 (26.2)
No	45 (73.8)
Gestational age	
≤22 weeks	5 (8.2)
Preterm (22–36 weeks)	26 (42.6)
Early term (37–38 weeks)	10 (16.4)
Full term (39–40 weeks)	12 (19.7)
Late term (41–42 weeks)	3 (4.9)
Unknown	5 (8.2)
Mode of delivery	
Normal vaginal	15 (24.6)
Planed CS[a]	3 (4.9)
Emergency CS[a]	32 (52.5)
Died during pregnancy	11 (18)

[a] Caesarean section.
[b] Supporting medical document or data was lacking in the data source.
[c] Empty box or insufficient information in the respective data source.

Among all direct causes, haemorrhage was the "initiating" event in the cascade of complications, which represented 29.5% (95% CI: 19.4–41.9) of all MM cases in our study. Nine MM cases died within 24 h, six died 2–6 days postpartum, and three died 7–42 days postpartum. Nine of these 18 cases had neither severe maternal diseases nor any severe pregnancy-related conditions. Fourteen of these cases had CS and died from postpartum bleeding. Seven of those 14 had no serious maternal- or pregnancy-related diseases recorded in their medical file. Only one MM case was attributed to uterine rupture, whereas six cases experienced placental abruption. Extensive blood loss was reported in seven MM cases (≥1500 ml); blood transfusion was provided in 11 cases (Table 4).

Hysterectomy was performed in 13 MM cases, among whom nine ended up with disseminated intravascular coagulation. Post-caesarean laparotomy was performed in five cases that suffered haemorrhage, but none of these cases received uterine artery embolisation as an alternative treatment. Pre-eclampsia was the dominant pregnancy-related disease associated with haemorrhage, mainly in combination with severe obesity and emergency CS. Moreover, severe obesity was observed in five out of 18 haemorrhage cases, anaesthesia complications in two of three, venous thromboembolism in four of six, and ectopic pregnancy one of two MM cases (Tables 3 and 4).

Of all 22 MM cases attributed to indirect causes of maternal death, seven died during pregnancy, three died 2–6 days postpartum, and 12 died 7–42 days postpartum (Table 5). The leading cause of indirect maternal death was infection (10 cases, comprising 45.5%); among them were leptospirosis (2 cases), pneumonia (2 cases), tuberculosis (2 cases), meningitis (2 cases), and hepatitis (1 case). Three became pregnant after a cancer diagnosis (acute leukaemia) and two had a diagnosis of malformations. Of those, four died during pregnancy and the fifth a few days after childbirth. Three MM cases died from complications of cardiovascular disease, three from suicide, and one case from complications due to a cholecystectomy in the postpartum period (Table 5).

Thirty-one percent of MM cases had incomplete medical records, i.e., missing ANC related data, autopsy data, and histology reports.

Discussion

This is the first study of MM that has been performed after the creation of the MCHCC in Georgia. We found that the share of direct causes of maternal death exceeded that of indirect causes of maternal death. Haemorrhage was the leading direct cause of maternal death, and infection was the most common indirect cause. The estimated MMR during our study period was 26.7 per 100,000 live births. This number confirms the relatively stable MMR reported by the country's official national statistics office for the last decade [11,13]. Moreover, it reflects the same level of MM recently reported from middle-income countries in Europe (Romania, Russian Federation, and Turkey), Central and East Asia (Armenia, Azerbaijan, Turkmenistan, and Uzbekistan), and Latin America (Costa Rica) [7,10,21,22,23]. However, the observed MMR in Georgia is double that of most high-income countries [1,24,25] and far from the ratio being targeted for 2030 in Georgia [13,14]. Obviously, some actions have already been taken to change the current MMR; although, tailored solutions based on evidence should be initiated to reach the desired goal before the deadline.

A notable finding was the proportion of direct and indirect causes of

Table 3
Direct causes of maternal death - major maternal, pregnancy, and delivery related events, excluding haemorrhage. Georgia, 2014–2017.

Time of death	Maternal condition	Pregnancy-related condition	Mode of delivery	Delivery-related condition	Postpartum events
In pregnancy	Obesity	Ectopic pregnancy	Not applicable	Not applicable	Not applicable
In pregnancy	None	Ectopic pregnancy	Not applicable	Not applicable	Not applicable
Delivery	None	Preeclampsia	Emergency CS[b]	Anaesthesia complications	Not applicable
Delivery	Obesity	None	Emergency CS[b]	Anaesthesia complications	Not applicable
7–42 days	Obesity	Preeclampsia	Emergency CS[b]	Anaesthesia complications	Oesophageal haemorrhage, sepsis
1st 24 h	None	None	Emergency CS[b]	Amniotic fluid embolism	Hysterectomy
1st 24 h	None	Preeclampsia	Emergency CS[b]	Amniotic fluid embolism	None
2–6 days	Anaemia	None	Vaginal	Amniotic fluid embolism	HELLP[a], DIC[c]
1st 24 h	None	None	Vaginal	None	Venous thromboembolism
2–6 days	Obesity	None	Emergency CS[b]	None	Venous thromboembolism
2–6 days	Obesity	None	Emergency CS[b]	None	Venous thromboembolism
7–42 days	Obesity	Preeclampsia	Emergency CS[b]	None	Venous thromboembolism
7–42 days	Obesity	None	Planned CS[b]	None	Venous thromboembolism
7–42 days	None	None	Emergency CS[b]	None	Venous thromboembolism
1st 24 h	None	Preeclampsia	Vaginal	Eclampsia	None
7–42 days	None	Eclampsia	Emergency CS[b]	None	HUS[d], hysterectomy, DIC[c]
7–42 days	None	HELLP[a]	Vaginal	Haemorrhage	Septic shock
7–42 days	None	HELLP[a]	Vaginal	None	Septic shock

[a] Haemolysis, elevated liver enzymes, and a low platelet count.
[b] Caesarean section.
[c] Disseminated intravascular coagulation.
[d] Haemolytic-Uremic Syndrome.

Table 4
Direct causes of maternal death - major maternal, pregnancy and delivery related events, cases with haemorrhage. Georgia 2014–17.

Time of death	Maternal condition	Pregnancy-related condition	Mode of delivery	Delivery-related condition	Blood loss (ml)	Postpartum events
1st 24 h	None	None	Emergency CS[a]	Haemorrhage	1300[b]	Hysterectomy
1st 24 h	None	None	Emergency CS[a]	Haemorrhage	Unknown	Hysterectomy, DIC[c]
1st 24 h	None	None	Emergency CS[a]	Haemorrhage, uterine rupture	Unknown[b]	None
1st 24 h	None	None	Vaginal	Haemorrhage, deep laceration	2500[b]	Laparotomy
1st 24 h	None	Preeclampsia	Emergency CS[a]	Haemorrhage, atony	Unknown	Hysterectomy, DIC[c]
1st 24 h	None	Preeclampsia /eclampsia	Vaginal	Haemorrhage	1800[b]	Hysterectomy
1st 24 h	Obesity	Preeclampsia	Emergency CS[a]	Haemorrhage, abrubtio placenta	1200[b]	Hysterectomy, DIC
1st 24 h	Obesity	Cervical cerclage, preeclampsia	Emergency CS[a]	Haemorrhage	600	None
1st 24 h	Obesity	Placenta praevia	Emergency CS[a]	Haemorrhage, abrubtio placenta	2200[b]	Hysterectomy
2–6 days	None	None	Emergency CS[a]	Haemorrhage, abrubtio placenta	2000[b]	DIC[c]
2–6 days	None	None	Emergency CS[a]	Haemorrhage, atony	2100[b]	Hysterectomy, DIC[c]
2–6 days	None	None	Vaginal	Haemorrhage, deep laceration	Unknown[b]	Hysterectomy, DIC[c]
2–6 days	None	None	Emergency CS[a]	Haemorrhage, atony	800	None
2–6 days	Obesity	None	Emergency CS[a]	Haemorrhage, abrubtio placenta	3500[a]	Hysterectomy, DIC[c]
2–6 days	Obesity	Preeclampsia	Emergency CS[a]	Haemorrhage, abrubtio placenta	2500[a]	Hysterectomy, DIC[c]
7–42 days	None	None	Vaginal	Retained products	Unknown[b]	Haemorrhage, hysterectomy
7–42 days	None	Preeclampsia	Planned CS[a]	None	Unknown[b]	HELLP[d], haemorrhage, hysterectomy
7–42 days	Anaemia	Preeclampsia	Emergency CS[a]	Haemorrhage, abrubtio placenta	Unknown	Haemorrhage, hysterectomy

[a] Caesarean section.
[b] Blood transfusion.
[c] Disseminated intravascular coagulation.
[d] Haemolysis, elevated liver enzymes, and a low platelet count.

maternal death (62% and 38%, respectively). It is important to analyse the distribution of these causes, as it gives an indication of the quality of antenatal, perinatal, postpartum, and continuum of care. When direct causes of maternal death exceed indirect causes, it suggests that obstetric care is substandard [26]. The study of global causes of maternal death and other retrospective studies have shown results similar to ours in other developing countries, where direct causes of maternal death account for around 70% of MM [5,22]. The proportions we report differ from the previous Georgian study, in which direct causes of maternal deaths accounted for 77% of MM cases and indirect causes accounted for 23% [18]. Our results indicate that Georgia is making progress in decreasing the MMR due to direct causes of maternal death; however, some aspects still need attention. The notably low number of high-risk pregnancies and co-morbidities we observed in MM cases are another indicator of substandard care, especially on an ANC level. Timely recognition of complications is important for correct diagnosis and treatment, which are important if MM is to be prevented [10,27]. To accelerate progress in the prevention of MM, Georgia should enhance optimal obstetric care, improve ANC guidelines to detect high-risk pregnancies and co-morbidities, and ensure that midwives and

Table 5
Indirect causes of maternal death - major maternal, pregnancy and delivery related events. Georgia 2014–17.

Time of death	Maternal condition	Pregnancy-related condition	Mode of delivery	Delivery-related condition	Postpartum events
In pregnancy	Acute leukaemia	None	Not applicable	Not applicable	Not applicable
In pregnancy	Ovarian cancer	None	Not applicable	Not applicable	Not applicable
In pregnancy	Cerebral malformation	None	Not applicable	Not applicable	Not applicable
2–6 days	Acute leukaemia	None	Emergency CS[c]	None	Cachexia
7–42 days	Cerebral malformation	None	Emergency CS[c]	None	Cerebral haemorrhage
In pregnancy	None	Pneumonia	Not applicable	Not applicable	Not applicable
In pregnancy	None	Leptospirosis, pneumonia, sepsis	Not applicable	Not applicable	Not applicable
In pregnancy	None	Leptospirosis, chorioamnionitis, sepsis	Not applicable	Not applicable	Not applicable
2–6 days	Multi resistant TB[a]	None	Vaginal	None	Acute respiratory distress
2–6 days	None	TB, preeclampsia	Emergency CS[c]	None	Acute respiratory distress
7–42 days	None	Pneumonia	Emergency CS[c]	None	Acute respiratory distress
7–42 days	None	Pneumonia	Emergency CS[c]	None	Acute respiratory distress
7–42 days	None	None	Vaginal	None	Meningitis
7–42 days	None	None	Unknown	None	Bacterial meningitis
7–42 days	Chronic hepatitis	None	Emergency CS[c]	None	Acute liver failure, sepsis
7–42 days	None	None	Emergency CS[c]	None	Complicated cholecystitis
7–42 days	CVD[b]	None	Emergency CS[c]	None	Cardiomyopathy
7–42 days	CVD[b]	None	Emergency CS[c]	None	Severe cardiac failure
7–42 days	Cardiomyopathy	None	Vaginal	None	Severe cardiac failure
In pregnancy	Mental disorder, suicide	None	Not applicable	Not applicable	Not applicable
7–42 days	None	None	Planned CS[c]	None	Mental disease, suicide
7–42 days	None	None	Vaginal	Retained products	Haemorrhage, sepsis, hysterectomy, suicide

[a] Tuberculosis.
[b] Cardiovascular disease.
[c] Caesarean section.

obstetricians complete special courses within the framework of their Continuous Medical Education. These measures could lower the proportion of MM due to direct causes of maternal death, and hence decrease the MMR.

Haemorrhage was the foremost direct cause of maternal death in our study. The latest study of global causes of maternal death showed that haemorrhage accounted for 27.1% of MM cases and represented the leading cause of maternal death worldwide [7]. In the present study, maternal death due to haemorrhage represented 29.5% of all MM cases, which is a common number in countries with a similar socio-development index [5]. Our findings correspond to previous information about leading causes of maternal death in Georgia, which also cited haemorrhage as the most common cause of death [13,18]. The majority of these cases occurred in low-risk pregnancies with no severe pregnancy-related conditions. However, the main mode of childbirth for these cases was emergency CS, and the indication for CS was lacking. Indeed, CS has intrinsic risks that can lead to a cascade of complications in both non-risk and high-risk pregnancies [28]. Therefore, the high fatality rate in these cases suggests inappropriate indications for CS, poor diagnostic skills, and lack of follow-up by responsible medical personnel during the post-operative period, which indicates necessity for future studies. Our results also suggest that there is a lack of active management in the third stage of labour to prevent haemorrhage, and that artery embolization is under-used as an alternative treatment for haemorrhage [28]. In general, haemorrhage is a preventable cause of maternal death, and recent studies have outlined ways to optimise the outcome of this condition. These publications promote a multidisciplinary team approach and the application of checklist-based protocols for the timely management of haemorrhage [13,28], neither of which was evidenced in our data. Additionally, the volume of blood lost or other justifications for such treatment did not consistently accompany reports of blood transfusion in our study. Nonetheless, study findings on haemorrhage are an additional indication of substandard care at all levels of reproductive services, including the inappropriate evaluation of risks, justification for blood transfusion, detection of co-morbidities, and lack of knowledge-based performance during obstetric emergencies. In order to further reduce the MMR, is it important to equip medical personnel with current knowledge and approaches to managing life-threatening conditions. These steps must be taken if we are to improve the quality of medical care for pregnant women and prevent haemorrhage as a major direct cause of maternal death.

Our study identified infection as the leading cause of indirect maternal death. Contrary to national improvements in access to antibiotic treatment, preventive vaccination, and advanced diagnostic and laboratory services, our results show a noticeably high proportion of MM attributable to infections [13,18]. Thus it may be possible to prevent mortality through more appropriate clinical solutions. However, our results lead us to believe that there is a fragmentation in continuous obstetric care, low quality of ANC, a lack of either continuous care or communication with sub specialists, and weak multidisciplinary approaches, all of which suggest substandard care. In their study of barriers to accessing adequate maternal care in Georgia, Miteniece et al. also indicated substandard care, along with gaps in clinical quality and staff skills, poor communication, and lack of continuous education programmes in the Georgian health care system [29]. After all, if a country is looking to accelerate its progress in preventing maternal death, it is not sufficient to improve ANC coverage; it is also necessary to ensure high quality and continuous care. Better medical performance and updated guidelines for provided services are needed, along with improved collaboration with specialists and timely referrals [10,15,23,30].

The major strength of this paper is the use of data from the MCHCC, along with validation from and enrichment with register-based data. In MM studies, Confidential Enquiries into Maternal Deaths and registries give researchers a great advantage, as they allow them to obtain information, analyse non-aggregated and consistence data, validate cases, and understand the full cascade of events [10,27]. Some of the limitations of this study include the primary data source, which was hospital records. Because of this, some problems arose in deciphering handwriting. Additionally, 31% of our MM cases had medical records with incomplete or missing information, which could have led to under-reporting; thus our results should be interpreted with caution. Moreover, our results showed that autopsy and forensic service are infrequent in Georgia, which is not unique, as many other developing countries face a similar problem, especially for ANC [31,32]. However, given the importance of decreasing the MMR, it is vital to have detailed, quality information on this topic [25]. Under the circumstances, insufficient medical files cannot guarantee a high-quality enquiry using MCHCC data. Indeed, this insufficiency led to the exclusion of 3 unclassifiable cases from our analyses as well. Furthermore, in-depth future studies on the quality of reproductive healthcare should address some specific questions (e.g. skills and competencies of medical personnel, quality of care at any level, provision and access to family planning, high proportion of CS and consistent of their indications). Limitation of the present study includes a small study sample with low MM in absolute numbers. Thus, results cannot fully address failure of reproductive healthcare system in specific health-related conditions (tuberculosis, hepatitis, and leukaemia). However, provided results are important to prioritize methodology for future studies and enhance them with the "near-miss" approach - identification and additional assessment of cases in which pregnant women survive certain complications [2,16].

Overall, our findings indicate the challenges Georgia faces in accelerating the reduction of MM. This evaluation of the causes of MM and classification of cases by direct and indirect causes of death with the use of national surveillance data may be used to generate new recommendations for clinical practice and policy improvement. This study has important implications for the quality enhancement of reproductive healthcare in Georgia. The present findings indicate the existence of weaknesses and gaps in the healthcare system that can only be improved through the collaboration of different stakeholders. Regular and systematic analyses, transparency, and involvement of professional associations, main decision makers, and healthcare authorities will strengthen reproductive healthcare and accelerate Georgia's progress to decrease MM. Moreover, austerity measures should be considered to ensure optimal obstetric care and family planning, to launch countrywide Continuous Medical Education for obstetricians, and to tailor trainings for midwives to tackle the knowledge gap. Measures should also be taken to trigger timely treatment or referral for multidisciplinary care and the establishment of routine autopsies in MM cases should be considered.

Conclusion

In Georgia, contrary to high-income countries, direct causes of death exceed indirect causes of death in MM cases, with haemorrhage and infections, respectively, being most common. The results suggest increasing efforts toward decreasing the MMR, where high-quality MM-related medical data and data completeness applications are crucial to obtain best medical measures and policies. The study findings are important to guide stakeholders and ensure that they implement optimal, continuous care and effective follow-up, and to accelerate progress in the reduction of MM in the country.

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Authors' contributions

NS co-developed the core idea and study design, collected data, reviewed all cases, conducted analyses, interpreted results, and wrote the article. EEA co-developed the core idea, participated in study design, in the interpretations of results, and in the revision of draft version of the article. NK collected data, reviewed all cases, interpreted results, and revised the draft version of the article. TB participated in the interpretations of results and in the revision of the draft version of the article. AG co-developed the core idea, developed study design, and participated in the interpretation of results and in the revision of the draft version of the article. All authors approved and agreed on the final version of the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Paper II

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SARS-CoV-2 infection during pregnancy and the risk of adverse maternal outcomes in the Republic of Georgia: a national birth registry-based cohort study.

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SARS-CoV-2 infection during pregnancy and the risk of adverse maternal outcomes in the Republic of Georgia: a national birth registry-based cohort study

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Abstract

Background Georgia experienced an increase in maternal deaths (MD) during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which warrants further investigation. This study aimed to assess associations between timing of SARS-CoV-2 infection during pregnancy and MD, post-delivery intensive care unit (ICU) admission, and caesarean section (CS) delivery.

Methods We performed a national birth registry-based cohort study of pregnant women who had completed 22 weeks of gestation and delivered between February 28, 2020, and August 31, 2022. The data were linked to coronavirus disease 2019 (COVID-19) testing, vital, and immunization registries. Pregnant women were classified into three groups: confirmed SARS-CoV-2 infection from conception through 31 days before delivery; confirmed infection within 30 days before or at delivery; and women negative for SARS-CoV-2 infection or without any test results (reference group). Multivariable logistic regression was used to calculate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results Among 111,493 pregnant women, 16,751 had confirmed infection during pregnancy, and 7,332 were fully vaccinated against COVID-19 before delivery. Compared to the reference group, those with confirmed infection within 30 days before or at delivery experienced increased odds of MD (aOR: 43.11, 95% CI, 21.99–84.55), post-delivery ICU admission (aOR: 5.20, 95% CI, 4.05–6.67), and CS delivery (aOR: 1.11, 95% CI, 1.03–1.20).

Conclusions Pregnant women in Georgia with confirmed SARS-CoV-2 infection within 30 days before or at delivery experienced a considerably higher risk of MD and post-delivery ICU admission and a slightly higher risk for CS delivery. Additionally, the results highlighted that most pregnant women were not vaccinated against COVID-19. These findings should alert stakeholders that adherence to public health preventive measures needs to be improved.

Keywords Registry-based cohort study, SARS-CoV-2 infection, Adverse maternal health outcomes, Caesarean section, Intensive care unit, Maternal death

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Background

At the onset of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), uncertainty existed regarding potential risks to pregnant women [1, 2]. Comprehensive evidence suggests pregnant women are a vulnerable group with an increased risk of adverse health outcomes following SARS-CoV-2 infection [3–5]. However, significant differences among nations in healthcare sector performance, testing policies, reporting accuracy, and adherence to preventive measures, including vaccination, impacted the official numbers of SARS-CoV-2 infected cases and complicate cross-country comparisons of the impact on population health. Moreover, studies on the adverse effects of SARS-CoV-2 infection in pregnant women have shown varying results owing to differences in study design, selection criteria for study groups, definitions of infections, and detection methods. The most recent evidence indicates that infection during pregnancy increases the risk of pregnancy complications (preterm delivery, caesarean section [CS] delivery, and intensive care unit [ICU] admission) and adverse outcomes (mortality and stillbirth) for both mothers and newborns [4, 6–8]. However, large representative studies on the health effects among pregnant women with and without SARS-CoV-2 infection are limited, and few have investigated the importance of the timing of SARS-CoV-2 infection. Studies that stratified mothers by the timing of infection did not present results on maternal outcomes in the different groups or lack a control group of non-infected women [9].

The first confirmed case of COVID-19 in the Republic of Georgia, a middle-income country, was detected on February 26, 2020. Despite a rapid national pandemic response, COVID-19 cases increased exponentially, and in December 2020, Georgia recorded the highest incidence in Europe [10, 11]. Georgia faced several waves of infection in 2021, the largest of which occurred between January and March 2022. Antenatal care (ANC) and delivery services were considered as essential health services that were to be provided without interruption during the pandemic. Improving maternal and newborn health has been a priority for Georgian public health authorities, who proposed a long-term strategy in 2017 to reduce the maternal mortality (MM) ratio to 12 per 100,000 live births by 2030 [12]. However, MM surged during the pandemic, with MM ratios increasing from 28.9 per 100,000 live births in 2019 to 71.8 per 100,000 live births in 2021 [13]. Georgia implemented mandatory SARS-CoV-2 testing during ANC and delivery. Although the country has several high-quality national health registries, no study has utilized these resources to assess whether pregnant women with SARS-CoV-2 infection experience an increased risk of adverse maternal outcomes compared to non-infected pregnant women. We hypothesized that women with SARS-CoV-2 infection close to or at delivery have a higher risk of adverse maternal outcomes than non-infected women and women with SARS-CoV-2 infection earlier in pregnancy. Therefore, this study aimed to assess the risk of maternal death (MD), post-delivery ICU admission, and CS delivery in relation to SARS-CoV-2 infection during pregnancy among women who had attained a gestational age (GA) of ≥22 weeks at the time of delivery.

Materials and methods

Data sources

The Georgian Birth Registry (GBR), a nationwide medical birth registry established in 2016 [14], registers all information during ANC, delivery, and subsequent hospital stay for mothers and newborns, and it covered 99.8% of all pregnancies in Georgia in 2021 [13–15]. The LabCov registry, launched in April 2020, electronically records the results of SARS-CoV-2 diagnostic tests, encompassing serological tests (antigen) and molecular tests (reverse transcription polymerase chain reaction), conducted by both private and state laboratories throughout the country. Individuals are registered with LabCov during sample collection and test results must be entered within 24 h of their availability [16, 17]. From June 2020, all pregnant women admitted to birth centers or hospitals were routinely tested for SARS-CoV-2 [17]. Pregnant women in Georgia have eight free-of-charge ANC visits in GA weeks < 13, 18, 26, 30, 34, 36, and 38 [18]. From October 2021, routine testing of pregnant women during ANC visits was implemented. The Immunization Electronic Module, implemented in 2019, registers all vaccinations performed in the country. The Vital Registration System records all deaths in the country and is considered highly complete with 100% coverage. The details of these national digital registration systems administered by the healthcare sector are described elsewhere [14, 15, 19].

Study population

Given our hypothesis that SARS-CoV-2 infection close to or at the time of delivery increases the risk of adverse maternal outcomes, we included data from all women who had attained GA week ≥ 22 at the time of delivery, as recorded in the GBR. This inclusion criterion was based on the international classification of abortion and delivery [20]. Our study included all women registered in the GBR who delivered between February 28, 2020, and August 31, 2022, totaling 111,493 individuals.

Exposure and covariates

Information regarding the testing and confirmation of SARS-CoV-2 infection status during pregnancy was obtained from LabCov. Pregnant women were then classified into three exposure groups: no confirmed infection during pregnancy (reference group), which included SARS-CoV-2-negative women and those with no recorded test results; confirmed infection from conception to 31 days before delivery; and confirmed infection within 30 days before or at delivery. The threshold of 30 days was chosen based on previous studies indicating that the virus takes an average of 30 days to clear from the body after a positive test result [21, 22]. Only the positive test result was considered in women with multiple confirmed SARS-CoV-2 infections during pregnancy.

We extracted information about relevant covariates, including sociodemographic characteristics (maternal age, education, and residency), BMI at the first ANC visit, obstetric history (plurality, adherence to ANC, and gestational diabetes), and GA at delivery, from the GBR. Education was classified as primary, secondary, higher, or unknown and residence was categorized as rural or urban. BMI at the first ANC visit was divided into four groups (18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2). Most obstetric history covariates were dichotomized (parity as primiparous or multiparous, plurality as singleton or multiple, and adherence to ANC and gestational diabetes as yes or no), but GA at delivery was divided into four groups (preterm ≤ 36 weeks; early term 37–38 weeks; full term 39–40 weeks; late term ≥ 41 weeks). Being fully vaccinated against COVID-19 was defined as receiving two full doses of vaccine either before SARS-CoV-2 infection (for women with confirmed infection) or at any time during pregnancy (for those with no confirmed infection). SARS-CoV-2 testing prior to pregnancy was limited to high-risk groups, specific professions, contacts, or those with a strong suspicion of infection, leading to inconsistent data on pre-pregnancy infection status. Consequently, this variable was omitted from the analysis owing to its unsystematic collection.

Outcomes

There were three main maternal outcomes in this study: MD, post-delivery ICU admission, and CS delivery. The standard definition of MD is a death at any time during pregnancy and up to 42 days after pregnancy termination [20]. In this study, we restricted the definition to the death of a pregnant woman who had attained a GA of 22 weeks and up to 42 days after delivery, since delivery was a prerequisite for our study hypothesis. Information on MD was extracted from the Vital Registration System, and information on maternal post-delivery ICU admission and CS delivery was extracted from the GBR. Post-delivery ICU admission was defined as any admission to the ICU (within or outside the location of the birthing facility) after delivery, and CS deliveries included both elective and emergency CS deliveries.

Statistical analyses

All statistical analyses were performed using STATA, version 17 (StataCorp, TX, USA). Nominal data are presented as frequencies and percentages. Continuous variables are presented as means and standard deviations.

Logistic regression analyses were performed to assess the association of SARS-CoV-2 infection during pregnancy with MD, post-delivery ICU admission, and CS delivery. Directed acyclic graphs (DAGs) were used to identify possible confounding factors in the assumed causal pathways between SARS-CoV-2 infection during pregnancy and MD, post-delivery ICU admission, and CS delivery. The relationships depicted between the variables included in the DAGs were based on previous literature and underlying theories (details in Supplementary material). Based on the DAGs, MD models were adjusted for age, education, BMI at the first ANC visit, parity, gestational diabetes, and COVID-19 vaccination status; post-delivery ICU admission models were adjusted for age, BMI at the first ANC visit, gestational diabetes, and COVID-19 vaccination status; and CS delivery models were adjusted for age, education, BMI at the first ANC visit, parity, and gestational diabetes (Supplementary Figs. 1–3). We also performed a sensitivity analysis for post-delivery ICU admission by excluding MDs and women who underwent CS delivery. Moreover, to ensure that the inclusion of women with no recorded SARS-CoV-2 test results did not bias the results, we performed additional sensitivity analyses in which we restricted the models for all three outcomes to women with recorded SARS-CoV-2 test results in LabCov during pregnancy (Supplementary Table 1). All results are presented as crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

Results

Among 111,493 pregnant women who gave birth in Georgia from February 28, 2020, to August 31, 2022, 13,800 (12.4%) had confirmed SARS-CoV-2 infection in early pregnancy (from conception through 31 days before delivery), and 2,915 (2.6%) had confirmed infection within 30 days before or at delivery.

Majority of the investigated characteristics showed similarities across the three exposure groups; the mean maternal age was approximately 29 years for all groups, most had secondary education, attended ANC, delivered at full term, and were not fully vaccinated against COVID-19 (Table 1). However, both groups of women with confirmed SARS-CoV-2 infection tended to have certain characteristics more frequently than those in the reference group. These characteristics included a higher

Table 1 Characteristics of pregnant women by SARS-CoV-2 infection status. The Georgian Birth Registry, February 28, 2020- August 30, 2022

	No confirmed SARS-CoV-2 infection (reference group) ***n*** **= 94,778***	**Confirmed SARS-CoV-2 infection in early pregnancy*** ***n*** **= 13,800***	**Confirmed SARS-CoV-2 infection within 30 days before or at delivery** ***n*** **= 2,915***
Maternal age, mean (SD)	28.9 (5.90)	29.6 (5.69)	29.4 (5.83)
Education, n (%)			
Primary	7,395 (7.8)	441 (3.2)	163 (5.6)
Secondary	38,869 (41.0)	5,227 (37.9)	1,161 (39.8)
Higher	29,922 (31.6)	5,221 (37.8)	995 (34.2)
Unknown	18,591 (19.6)	2,911 (21.1)	594 (20.4)
Residency, n (%)			
Urban	68,952 (72.8)	11,047 (80.0)	2,181 (74.9)
Rural	25,750 (27.1)	2,753 (20.0)	734 (25.1)
Unknown	76 (0.1)	0 (0)	0 (0)
BMI at first ANC visit, n (%)			
<18.5	5,965 (6.6)	846 (6.3)	185 (6.6)
18.5–24.9	52,862 (58.5)	7,924 (58.8)	1,581 (56.3)
25–30	20,577 (22.8)	2,997 (22.3)	682 (24.3)
>30	10,926 (12.1)	1,698 (12.6)	361 (12.8)
Parity, n (%)			
Primiparous	36,508 (38.5)	5,621 (40.7)	1,166 (40.0)
Multiparous	58,270 (61.5)	8,179 (59.3)	1,749 (60.0)
Plurality, n (%)			
Singleton	93,167 (98.3)	13,585 (98.4)	2,865 (98.3)
Multiple	1,611 (1.7)	215 (1.6)	50 (1.7)
Adherence to ANC**, n (%)			
No care	4,400 (4.6)	313 (2.3)	85 (2.9)
Attended	90,378 (95.4)	13,487 (97.7)	2,830 (97.1)
Gestational age during first ANC visit, mean (SD)	10.1 (4.64)	9.8 (3.89)	9.6 (3.65)
Gestational diabetes, n (%)			
Yes	143 (0.2)	31 (0.2)	7 (0.2)
No	94,634 (99.8)	13,769 (99.8)	2,906 (99.8)
Fully vaccinated***, n (%)			
Yes	5,084 (5.4)	1,739 (12.6)	310 (10.6)
No	89,694 (94.6)	12,057 (87.4)	2,605 (89.4)

* Not all numbers add up to the total because of missing observations in the Georgian Birth Registry

** Antenatal care

*** Receiving two full doses of vaccine either before SARS-CoV-2 infection (for women with confirmed infection) or any time during pregnancy (for those with no confirmed infection)

likelihood of attaining a higher education level, living in urban areas, attending ANC, being primiparous, and being fully vaccinated against COVID-19. Gestational diabetes was rare and was equally distributed across the exposure groups.

In total, 39 women died during the study period. Of these, 23 (59%) had confirmed SARS-CoV-2 infection during pregnancy, and none were fully vaccinated. Among the 649 women admitted to the post-delivery ICU, 37 (5.7%) were fully vaccinated. Women with SARS-CoV-2 infection within 30 days before or at delivery were more likely to experience MD (0.75% vs. 0.02%) and post-delivery ICU admission (2.57% vs. 0.54%) than those in the reference group (Table 2). Furthermore, compared to the reference group, both groups of women with confirmed infection had a higher likelihood of CS delivery (44.8% and 45.9% vs. 41.9%, Table 2).

After adjusting for confounding factors, the odds of MD were almost 43 times higher among women with confirmed SARS-CoV-2 infection within 30 days before or at delivery compared to the reference group (aOR, 43.11; 95% CI, 21.99–84.55). In contrast, women with confirmed infection in early pregnancy did not experience higher odds of MD than the reference group (aOR, 0.47; 95% CI, 0.06–3.59). The odds of post-delivery ICU admission were five times higher among women with confirmed SARS-CoV-2 infection within 30 days before or at delivery (aOR, 5.20; 95% CI, 4.05–6.67) compared to the reference group, whereas women with confirmed SARS-CoV-2 infection in early pregnancy had odds of

Table 2 Unadjusted and aORs and 95% CIs for the association between SARS-CoV-2 infection during pregnancy and maternal death, post-delivery intensive care unit admission, and caesarean section delivery

	No confirmed SARS-CoV-2 infection (reference group) *n* = 94,778		Confirmed SARS-CoV-2 infection in early pregnancy* *n* = 13,800			Confirmed SARS-CoV-2 infection within 30 days before or at delivery *n* = 2,915		
Outcome	**n**	**OR/aOR**	**n**	**OR (95%CI)**	**aOR (95%CI)**	**n**	**OR (95%CI)**	**aOR**
Maternal death[a]	16	1.0/1.0	1	0.43 (0.06–3.24)	0.47 (0.06–3.59)	22	45.03 (23.62–85.84)	43.11 (21.99–84.55)
Post-delivery intensive care unit admission[b]	509	1.0/1.0	65	0.88 (0.68–1.14	0.93 (0.71–1.21)	75	4.89 (3.83–6.25)	5.20 (4.05–6.67)
Caesarean section delivery[c]	39,720	1.0/1.0	6,182	1.12 (1.09–1.17)	1.07 (1.03–1.11)	1,337	1.17 (1.09–1.26)	1.11 (1.03–1.20)

aOR – adjusted odds ratio; 95% CI – 95% confidence interval; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

[a]The aOR was adjusted for age, education, parity, body mass index at first antenatal care visit, gestational diabetes, and COVID-19 vaccination.

[b]The aOR was adjusted for age, body mass index at first antenatal care visit, gestational diabetes, and COVID-19 vaccination.

[c]The aOR was adjusted for age, education, parity, body mass index at first antenatal care visit, gestational diabetes, and COVID-19 vaccination.

*From conception until 31 days before delivery.

post-delivery ICU admission that were similar to those in the reference group (aOR, 0.93; 95% CI, 0.71–1.21). Notably, the increased odds of post-delivery ICU admission in women with confirmed SARS-CoV-2 infection within 30 days before or at delivery remained high after the exclusion of women with the outcomes of MD (aOR, 4.44; 95% CI, 3.37–5.88) and CS delivery (aOR, 5.39; 95% CI, 3.51–8.27, Supplementary Table 1). Further, women with confirmed SARS-CoV-2 infection within 30 days before or at delivery had 11% higher odds of CS delivery (aOR, 1.11; 95% CI, 1.03–1.20) compared to the reference group (Table 2). Likewise, women with confirmed SARS-CoV-2 infection in early pregnancy experienced 7% higher odds of CS delivery (aOR, 1.07; 95% CI, 1.03–1.11). After restricting the analyses to women with recorded test results in LabCov, the associations between confirmed infection within 30 days before or at delivery and MD (aOR, 36.6; 95% CI, 16.6–80.7), post-delivery ICU admission (aOR, 4.80; 95% CI, 3.68–6.26), and CS delivery (aOR, 1.10; 95% CI, 1.01–1.19) remained strong.

Discussion

This paper presents results from a national birth registry-based cohort study, conducted in a middle-income country, evaluating the risks of SARS-CoV-2 infection at different times during pregnancy in relation to CS delivery and adverse maternal outcomes. Our results clearly demonstrate that pregnant women with confirmed SARS-CoV-2 infection within 30 days before or at delivery had a substantially increased risk of MD and post-delivery ICU admission. Compared to the reference group, their odds of MD and post-delivery ICU admission were 43 and 5 times higher, respectively. The odds of CS delivery also increased slightly. Notably, women infected in early pregnancy (conception to 31 days before delivery) and attained 22 weeks of gestation before delivery did not exhibit increased odds of MD or post-delivery ICU admission compared to the reference group, suggesting that the timing of SARS-CoV-2 infection during pregnancy is a clear determinant of maternal risk. Few studies have categorized pregnant women based on the timing of SARS-CoV-2 infection, an important factor in our study. Our results have profound implications and should urge stakeholders to accelerate targeted preventive measures in Georgia to avoid infection during pregnancy.

Our results showing increased odds of MD in pregnant women with confirmed SARS-CoV-2 infection within 30 days before or at delivery align with previous studies that reported increased MD during the pandemic compared to the pre-pandemic period [23–25]. However, these studies did not include individual-level data. Our results also align with those of previous original studies, a large-scale multinational study, and systematic reviews of studies with individual-level data on SARS-CoV-2 infection in pregnant women [6, 8, 26–31]. While these studies compared MD risk in infected and uninfected women, we additionally demonstrated that the timing of infection during pregnancy is a clear determinant of risk. Thus, ignoring the timing of infection may obscure the negative effects of SARS-CoV-2 infection. In contrast to our findings, a national registry-based study from Denmark found no association between SARS-CoV-2 infection and MD on studying SARS-CoV-2-positive and -negative pregnant women [32]. Our findings also differ from those of a Nordic study that compared infected pregnant women to pregnant women in the pre-pandemic period [33] and from systematic reviews that covered the early period of the pandemic [26, 34]. However, these results are not surprising, given the disparities in resources between high-income and low- or middle-income countries which can influence the adverse effects of the virus on maternal health. Moreover, some studies included in the systematic reviews were performed in the early phases of the pandemic, when less transmissible variants of the virus were circulating, resulting in fewer infected women. Our results suggest that SARS-CoV-2 infection within 30 days before or at delivery significantly contributed to MD in Georgia during the study period. Reduced quality of care during the first wave of infection when the number of cases increased exponentially might explain negative outcomes. However, other factors like lack of staff due to infection and redeployment of staff to support COVID-19 patients may also explain our results. As healthcare systems and pandemic responses differed across countries, study results from different parts of the world vary.

In our study, the odds of post-delivery ICU admission remained almost 5.5 times higher in women with confirmed SARS-CoV-2 within 30 days before or at delivery compared to the reference group, even after excluding women who experienced MD and CS deliveries. In contrast, SARS-CoV-2 infection during early pregnancy did not increase the odds of post-delivery ICU admission, possibly due to sufficient recovery time before delivery. Contrary to initial reports of no serious negative maternal outcomes [26, 32], studies based on data from the later stages of the pandemic are consistent with our findings of increased odds of post-delivery ICU admission in SARS-CoV-2-positive women around the time of delivery [6–8, 30, 31]. Although most studies agree that SARS-CoV-2 infection during pregnancy increases risk of ICU admission, the strength of this association varies, possibly due to differences in study designs and sample sizes. As with MD, the increased risk of post-delivery ICU admission in SARS-CoV-2-infected pregnant women may be due to medical, organizational, and economic factors. In-depth investigations are needed to untangle the individual contributions of these factors to prevent future delivery complications in these women.

Our analysis also revealed that women with confirmed SARS-CoV-2 infection within 30 days before or at delivery had an 11% higher odds of CS delivery than those in the reference group. Additionally, women with confirmed SARS-CoV-2 infection in early pregnancy had slightly increased odds of CS delivery compared with the reference group. Our results are in line with those of a recent meta-analysis indicating a 16% increased risk of CS delivery in SARS-CoV-2-positive women compared to SARS-CoV-2-negative women [8], although other studies have reported no association between SARS-CoV-2 infection in pregnancy and CS delivery [6, 35]. Thus, the association between SARS-CoV-2 infection and CS delivery may vary across countries owing to different clinical management approaches for COVID-19-infected pregnancies.

Another important aspect revealed in our study was the low proportion of pregnant women in Georgia who were fully vaccinated against COVID-19. The preventive effect of vaccination against the development of severe disease and death is unquestionable [36–38]. Recent studies have indicated the significant benefit of COVID-19 vaccination for pregnant women, similar to the general population [37–40]. Although we did not assess the risk of maternal outcomes according to vaccination status, 59% of the women who died in our study were SARS-CoV-2-positive and none were vaccinated against COVID-19. Moreover, only 5.7% of pregnant women admitted to the ICU were vaccinated. These observations underscore the need for future research on the influence of vaccination status on adverse maternal outcomes in SARS-CoV-2 infected pregnant women in Georgia.

The main strength of this study lies in the utilization of the GBR, a national population-based birth registry. Its use minimized selection bias, because registration in the GBR is mandatory by law. MDs were extracted from the Vital Registration System, which has close to 100% coverage. The national testing strategy of frequently and routinely testing pregnant women for SARS-CoV-2 significantly improved the accuracy of our exposure classification and determination of the timing of infection. However, this study had several limitations. Given our study hypothesis that pregnant women are at a higher risk of adverse maternal outcomes when infected with SARS-CoV-2 close to or at delivery, we only included women who attained 22 weeks of gestation. Hence, women who died before GA week 22 were not eligible for our study because delivery before GA week 22 was defined as abortion. This may have affected our results. Moreover, from the beginning of the pandemic until the implementation of routine testing strategies, a considerable proportion of women with undetected SARS-CoV-2 infection in early pregnancy may have been misclassified as part of the reference group. Even after routine testing was implemented during ANC, pregnant women with COVID-19 that resolved between ANC visits would have remained undetected. As shown in other studies, it was not possible to overcome the potential misclassification of participants who were infected but were never tested [41], which may have affected our results. Furthermore, lack of information on the viral variants, infection status prior to pregnancy, severity of SARS-CoV-2 infection, socioeconomic status, and ethnicity could potentially confound the relationship between SARS-CoV-2 infection and maternal outcomes. Moreover, gestational diabetes is rare and may be under-reported. Finally, our results showed the impact of SARS-CoV-2 infection on adverse maternal health outcomes in pregnant women; however, we had no information regarding the specific causes of death. Further in-depth study is recommended after clinical audits have been finalized and related information on all MDs during the study period has been collected.

Conclusion

In Georgia, pregnant women with SARS-CoV-2 infection detected within 30 days before or at delivery had a significantly higher risk of MD and post-delivery ICU admission, along with a modest increase in CS delivery compared to uninfected women. Infection earlier in pregnancy did not increase these risks. As most participants were unvaccinated, these results highlight the urgent need for public health efforts to promote COVID-19 preventive measures among pregnant women.

Abbreviations

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
COVID-19	coronavirus disease 2019
CS	caesarean section
ICU	intensive care unit
ANC	antenatal care
MD	maternal death
MM	maternal mortality
GA	gestational age
GBR	Georgian Birth Registry
BMI	body mass index
DAGs	directed acyclic graphs
aORs	adjusted odds ratios
CIs	confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-024-06329-x.

Supplementary Material 1

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Author contributions

All the authors contributed to the methodology, analysis, writing, and editing of the manuscript. All authors approved the final version of the manuscript and agreed to be responsible for all the provided information. CR, TM, TB, and AG supervised the study. NS, CR, and TM summarized the national datasets and contributed to data collection and curation. NS drafted the manuscript and amended it according to the feedback from all authors.

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Data availability

According to Georgian legislation, data from the central health registries can be used for research purposes if personal data are not shared. Appropriate ethical and legal approval are required to meet the criteria for access before requesting data, and only anonymized data can be shared. Researchers can contact the National Center for Disease Control and Public Health in Georgia (ncdc@ncdc.ge) or the corresponding author (natia.skhvitaridze@uit.no) for assistance on how to apply for access to data from central health registries.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of National Center for Disease Control and Public Health approved the legal aspects of the study (IRB #2023-001). In addition, Regional Committees for Medical and Health Research Ethics in Northern Norway approved the protocol (Ref: 577179, 20/02/2023). All data included in this paper were extracted from the national population registries and anonymized before the researchers received the dataset; registration in the national registries is mandatory by law; citizens cannot refuse to be registered. Consent was not obtained from study subjects, as was deemed unnecessary according to national regulation (according the Order of Minister of Georgia N01-26/ნ "About the rules of production and delivery of medical statistics", https://matsne.gov.ge/en/document/view/4509878?publication=0). Therefore, informed consent was not collected. This article is in line with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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Publisher's Note

Paper III

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Anemia during pregnancy and adverse maternal outcomes in Georgia – a birth registry-based cohort study.

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Anemia during pregnancy and adverse maternal outcomes in Georgia – a birth registry-based cohort study

Anemia in pregnancy and maternal outcomes

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Abstract

Background Anemia in pregnancy is an important public health challenge; however, it has not been thoroughly studied in Georgia. We assessed the prevalence of anemia during pregnancy across Georgia and the association between anemia in the third trimester of pregnancy and adverse maternal outcomes.

Methods We used data from the Georgian Birth Registry and included pregnant women who delivered between January 1, 2019, and August 31, 2022 (n=158,668). The prevalence of anemia (hemoglobin (Hb) < 110 g/L) at any time during pregnancy was calculated per region. Women in the third trimester were classified into three groups, based on their lowest measured Hb value: no (Hb ≥110 g/L, reference group); mild (Hb 100-109 g/L); and moderate to severe anemia (Hb <99 g/L). Adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were calculated for the associations between anemia status and post-delivery intensive care unit (ICU) admission and preterm delivery.

Results The prevalence of anemia occurring at least once during pregnancy was 40.6%, with large regional differences in anemia prevalence (25.1%–47.0%). Of 105,811 pregnant women with Hb measurements in the third trimester, 71.0% had no anemia; 20.9%, mild anemia; and 8.1%, moderate or severe anemia. The odds of post-delivery ICU admission did not increase linearly with decreasing Hb value (*P* for trend .13), and the relationship was inverse for preterm delivery (*P* for trend .01).

Conclusions A considerable proportion of pregnant women in Georgia have anemia during pregnancy, and the prevalence and quality of reporting differ across regions. Anemia occurring in the third trimester did not substantially increase the odds of maternal ICU admission or preterm delivery. To accelerate national progress toward the Sustainable Development Goals and mitigate

the consequences of anemia, equal countrywide access to high-quality antenatal care programs and complete registration of Hb values should be ensured.

Introduction

Anemia in pregnancy, defined as a hemoglobin (Hb) level below 110 g/L [1], is an important public health challenge, affecting 30-60% of pregnancies globally, and mainly women in the third trimester [2-4]. Iron deficiency, generally due to a low dietary iron intake, is the most common cause of anemia. It has been estimated that iron deficiency anemia contributes almost 22% to maternal deaths worldwide, most occurring in low-income countries [5]. Several systematic reviews and meta-analyses have reported that anemia in pregnancy significantly increases the risk of preterm delivery [6-8]. Moreover, increased risk of maternal mortality and other adverse outcomes, such as severe post-partum hemorrhage, maternal shock, and admission to the post-delivery intensive care unit (ICU), have also been associated with anemia [9-11]. However, recent studies have reported both positive and inverse associations between anemia in pregnancy and several adverse maternal outcomes. This could be due to differences in screening, follow-up approaches, and treatment regimens, and the contradictory results pose significant challenges for decision- and policymakers in implementing evidence-based recommendations [2, 12, 13].

The diagnosis of anemia is straightforward but the disease is silent, with few physical symptoms, and it is much more complex to identify the underlying causes of anemia [14]. Many women in low- and middle-income countries may also have had undiagnosed anemia before the pregnancy [13]. Initiated by the World Health Organization (WHO), the World Health Assembly approved global targets for maternal, infant, and young child nutrition in 2012 with a commitment to reduce the prevalence of anemia in women of reproductive age by 50% before 2025 [15]. In 2020, ending anemia in women aged 15–49 was added to the Sustainable Development Goals indicator 2.2.3 [16]. The deadline for the global targets has been extended to 2030 [17]. Despite this, knowledge about global progress toward the anemia target is scarce, and global comparisons are challenged by differences in the reporting of anemia prevalence across countries [18]. Thus, the disease remains underdiagnosed and understudied [19].

Georgia is an upper-middle-income country in the Caucasus with a population of 3.7 million [20]. Reducing maternal anemia and improving reproductive healthcare are national priorities in Georgia. However, little is known about the prevalence of anemia in the country and its impact on maternal morbidity. The most recent study on this subject is the Georgian National Nutrition Survey conducted in 2009, in which 25.6% of pregnant women had anemia [21]. This study aimed to provide information about the national and regional prevalence of anemia in pregnant women in Georgia and to evaluate the associations between anemia in the third trimester and maternal transfer to the post-delivery ICU and preterm delivery.

Materials and methods

The Georgian Birth Registry

Following World Health Organization recommendations, eight antenatal care (ANC) visits are free of charge for Georgian citizens [22]. Most pregnant women in Georgia attend at least one ANC visit (95.8% in 2021) and deliver in a health facility (99.8% in 2021) [23]. The Georgian Birth Registry (GBR) contains countrywide information of all medical facility-based deliveries and ANC visits [24, 25]. The coverage of newborns registered in the GBR was 99.8% in 2021 [26]. Registering information in the GBR is mandatory for the involved healthcare facilities. The GBR includes many variables, including demographic characteristics, disease history, and information about the current pregnancy up to post-delivery hospital discharge [26]. The GBR also includes Hb levels registered during ANC visits. According to national guidelines, the first ANC visit, recommended before gestational age (GA) week 13, should include a full blood count, including Hb measurement. Hb levels should be measured again at the third ANC visit at GA week 26, the fourth ANC visit at GA week 30, and the sixth ANC visit at GA week 36 [27]. The study data were accessed for research purposes on July 12, 2023.

Study sample

We initially included the data of all women registered in the GBR who gave birth between January 1, 2019, and August 31, 2022, who were at least at GA 22 weeks (n=166,043). We excluded women who did not attend ANC during their pregnancy (n=7,375), resulting in an analytical sample of 158, 668 women. Of these, 28,709 women attended ANC, but had no or no reliable Hb measure registered in the GBR. To calculate the national and regional prevalence of anemia among women who delivered after week 22, we used the data of all women who had at least one Hb measurement during the pregnancy (n=129,959). To study the association between anemia severity, post-delivery ICU admission, and preterm delivery, we included only women with at least one Hb measurement in the third trimester (GA week 28 and onwards; n=105,811 women). For the third trimester cutoff, we followed the recommendations of the National Institute for Health and Care Excellence, UK [28] (Fig. 1).

Figure 1. Flow chart of the study sample

Exposure and covariates

Hb levels ≤40 g/L or ≥180 g/L were considered implausible [29] and were recoded as "missing." Women were considered to have anemia at any time during pregnancy if their lowest recorded Hb level was <110 g/L. We classified pregnant women into anemia severity groups based on their lowest measured Hb value at any time during pregnancy (total study sample) or during the third trimester (sub-sample used for the regression analysis): no anemia (Hb ≥110 g/L, reference group); mild anemia (Hb 100–109 g/L); moderate (Hb 70–99 g/L) and severe (Hb <70 g/L) anemia. The moderate and severe anemia groups were combined in the regression analysis because of the limited number of women in the severe anemia group. The thresholds for Hb levels were based on the WHO recommendation for anemia classification [1].

Information on sociodemographic characteristics (maternal age, residency, and education), year of delivery, obstetric history (frequency of ANC, parity, plurality, mode of delivery, and bleeding during pregnancy), body mass index (BMI) at the first ANC visit before GA week 13, and GA at the lowest recorded Hb value were extracted from the GBR. Maternal age was defined as the mother's age at delivery. Residence was categorized as rural, urban, or unknown, and education was classified as primary, secondary, higher, or unknown. We dichotomized most covariates related to obstetric history: parity as primiparous or multiparous, plurality as singleton or multiple, and bleeding during pregnancy as yes or no, based on the International Classification of Disease version 10 (ICD10) code O 20.0 [30]. Number of ANC visits was divided into three groups (<4 visits; 4-8 visits; >8 visits), and the mode of delivery was grouped into two - cesarean section or vaginal delivery. BMI at the first ANC visit <GA week 13 was divided into five groups according to the WHO classification of body weight status (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–30 kg/m^2, >30 kg/m^2 and missing BMI before GA week 13) [31].

Outcomes

We extracted information on the two main outcomes, post-delivery ICU admission and preterm delivery from the GBR. Post-delivery ICU admission was defined as any admission to the post-delivery ICU during or after delivery. Preterm delivery was defined as delivery before GA week 37.

Ethics and consent

Regional Committees for Medical and Health Research Ethics in Northern Norway approved the study protocol (Ref: 577179, 20/02/2023). All data included in this study were extracted from the GBR and anonymized before the researchers received the data. Registration in the national registries is mandatory by law, and citizens cannot refuse registration. Consent was not obtained from the study participants as it is deemed unnecessary according to national regulations [32].

The study reporting is in line with the Helsinki declaration and the strengthening the reporting of observational studies in epidemiology (STROBE) guideline.

Statistical analysis

We calculated the period prevalence (2019–2022) of anemia at any time during pregnancy per region by dividing the number of pregnant women in each region with at least one Hb measurement of < 110 g/L (anemia cases) by the total number of women in that region with at least one valid Hb measurement registered in the GBR during the same study period. Descriptive statistics for anemia testing status are presented as frequencies and percentages for nominal variables and means and standard deviations for continuous variables.

Binary logistic regression assessed the associations between anemia (three exposure groups) in the third trimester and post-delivery ICU admission and preterm delivery. We estimated crude associations and associations adjusted for confounding factors. We drew directed acyclic graphs (DAGs) to identify possible confounding factors between anemia during pregnancy and post-delivery ICU admission and preterm delivery. The relationships depicted between the variables included in the DAGs are based on previous literature and the underlying theory (details are described in Supplementary file 1 and 2). The DAGs assumed that anemia had a causal effect on the outcomes. Based on the DAGs, the post-delivery ICU admission model was adjusted for age, BMI, bleeding during pregnancy, cesarean section delivery, and parity, and the preterm delivery model was adjusted for age, education, BMI, bleeding during pregnancy, and plurality. The results were presented as crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs). We included continuous Hb values in the logistic regression models to test for linear trends and extracted the *P* value, corresponding to one incremental change in Hb. The significance threshold was set at .05. All statistical analyses were performed using STATA version 17 (StataCorp, TX, USA).

Results

During the study period, 52,826 pregnant women had anemia (Hb <110 g/L) at least once during pregnancy, translating into a prevalence of 40.6%. Of these, 28.3%, 11.9 %, and 0.5% had mild, moderate, and severe anemia, respectively (Supplementary Table 1). Only 10,884 (8.4%) pregnant women had an Hb measurement before GA week 13, and 28,709 (18.1%) pregnant women had no Hb measurement during the entire pregnancy, although they attended ANC (Supplementary Table 1). Having two Hb measurements during pregnancy was the most common scenario (n=67,425, 51.9%).

The prevalence of anemia differed across the 12 administrative regions in Georgia and was lowest in Samtskhe-Javakheti (25.1%) and Racha (34.4%) and highest in Adjara (47.0%) and Kvemo Kartli (46.5%) (Fig. 2).

The proportion of women with no or no reliable Hb measurements during pregnancy also varied considerably across regions; it was highest in Samegrelo and Zemo Svaneti, where 33.3% of pregnant women had no registered Hb measurement and lowest in Samtskhe-Javakheti (7.1%) and Imereti (8.0%) (Supplementary Table 2). The number of women who did not attend ANC also varied by region; Mtskheta-Mtianeti and Kakheti had the highest proportions of non-attendance (6.6% and 6.1%, respectively) and Adjara, Imereti, and Samtskhe-Javakheti had the lowest proportions (2.6%) (Supplementary Table 3).

Figure 2. Anemia prevalence in Georgian regions, 2019-2022

Of the 105,811 included women with Hb measurement in their third trimester, 71.0% had no anemia, 20.9% had mild anemia, and 8.1% had moderate or severe anemia (Table 1). The third trimester prevalence of anemia varied by year and was highest in 2019 (25.9% and 11.5% for mild and moderate/severe anemia, respectively) and lowest in 2022 (17.3% and 5.9% for mild and moderate/severe anemia, respectively). The mean maternal age was around 28 years for all anemia groups. Most women lived in urban areas, had secondary education, attended between four and eight ANC visits, were normal weight, multipara, had a singleton pregnancy, and delivered vaginally. Notably, mild anemia was mostly diagnosed at GA week 35, and moderate/severe at GA week 34. Women with anemia in the third trimester were more likely to have more than eight ANC visits, have a BMI below 18.5 kg/m^2 at GA week <13, and be multiparous compared to women with no anemia in the third trimester. Bleeding during pregnancy was rare in all pregnant women and was almost equally distributed across all three anemia groups. Characteristics according to anemia status for the total study sample (Supplementary Table 1) were similar to those of the subsample of women with Hb measurement in the third trimester.

Table 1. Maternal Baseline Characteristics by Anemia Status During Third Trimester of Pregnancy

Characteristics	No anemia >110 g/L	Mild 100-109 g/L	Moderate & Severe <99 g/L
n (row, %)	75,114 (71.0)	22,122 (20.9)	8,575 (8.1)
Year of delivery, n (row, %)			
2019	18,339 (62.6)	7,579 (25.9)	3,367 (11.5)
2020	21,185 (72.0)	5,911 (20.1)	2,324 (7.9)
2021	22,218 (74.8)	5,624 (18.9)	1,852 (6.3)
2022	13,372 (76.8)	3,008 (17.3)	1,032 (5.9)
Age, mean (SD)	28.3 (5.68)	28.1 (5.75)	27.8 (5.77)
Residency, n (%)			
Urban	55,531 (73.9)	16,495 (74.6)	6,325 (73.8)
Rural	19,578 (26.1)	5,625 (25.4)	2,250 (26.2)
Unknown	5 (0.01)	2 (0.01)	0 (0.0)
Education, n (%)			
Primary	4,470 (6.0)	1,501 (6.8)	731 (8.5)
Secondary	30,879 (41.1)	9,594 (43.4)	3,687 (43.0)
Higher	27,221 (36.2)	7,330 (33.1)	2,479 (28.9)
Unknown	12,521 (16.7)	3,697 (16.7)	1,678 (19.6)
ANC visits, n (%)			
< 4	1,676 (2.2)	556 (2.5)	321 (3.7)
4-8	55,742 (74.2)	15,980 (72.2)	6,037 (70.4)
>8	17,696 (23.6)	5,586 (25.3)	2,217 (25.9)
BMI, n (%)[1]			
<18.5	4,987 (6.8)	1,565 (7.3)	610 (7.5)
18.5-24.9	43,338 (59.4)	12,948 (60.7)	5,077 (62.1)
25-30	16,052 (22.0)	4,618 (21.7)	1,646 (20.2)
>30	8,594 (11.8)	2,194 (10.3)	839 (10.3)
Parity, n (%)			
Nullipara	31,606 (42.1)	8,130 (36.8)	2,913 (34.0)
Multipara	43,508 (57.9)	13,992 (63.2)	5,662 (66.0)
Plurality, n (%)			
Singleton	74,424 (99.1)	21,887 (99.0)	8,455 (98.6)
Multiple	690 (0.9)	235 (1.0)	120 (1.4)
GA at lowest Hb value, mean (SD)	35.5 (1.70)	34.9 (2.27)	34.7 (2.47)

Lowest recorded Hb value, mean (SD)	118 (0.83)	104 (0.31)	90 (1.00)
Bleeding during pregnancy, n (%)			
Yes	1,166 (1.6)	451 (2.0)	165 (1.9)
No	73,948 (98.4)	21,671 (98.0)	8,410 (98.1)
Mode of delivery, n (%)			
CS	30,202 (40.2)	9,031 (40.8)	3,656 (42.6)
Vaginal	44,912 (59.8)	13,091 (59.2)	4,919 (57.4)

[1] 3,343 observations are not having BMI measures

Among women with at least one Hb measurement in the third trimester, 558 were admitted to the post-delivery ICU, and the proportions were relatively similar across the anemia groups (no anemia:0.5%, mild and moderate/severe anemia:0.6%) (Table 3). Furthermore, 3,411 women delivered preterm, and the proportion of preterm deliveries was similar in all exposure groups (3.2% in the non-anemia, mild, and moderate/severe anemia groups). After adjustments for confounding factors, women with mild or moderate/severe anemia experienced higher odds of post-delivery ICU admission than the reference group (aOR, 1.19; 95% CI, 0.97–1.46 and aOR, 1.24; 95% CI, 0.93–1.66, respectively), although the association was non-significant with a .05 threshold, and there was no sufficient evidence for a linear trend (*P* for trend = .13). In contrast, we observed a linear inverse association between anemia and preterm delivery (mild: aOR, 0.95; 95% CI 0.87-1.04; moderate and severe: aOR, 0.93; 95% CI 0.82-1.06, respectively, and *P* for trend= .01).

Table 2. Unadjusted and aORs and 95% CIs for the association between anemia during pregnancy and post-delivery ICU admission and preterm delivery

	Non anemia (reference group) n=75,114		**Mild 100-109 g/L n=22,122**			**Moderate & Severe <99 g/L n=8,575**			***p*-value for linear trend**
Outcome	**n (%)**	**OR/aOR**	**n (%)**	**OR (95%CI)**	**aOR (95%CI)**	**n (%)**	**OR (95%CI)**	**aOR (95%CI)**	
Post-delivery ICU admission	377 (0.5)	1.0/1.0	129 (0.6)	1.16 (0.95-1.42)	1.19 (0.97-1.46)	52 (0.6)	1.21 (0.90-1.62)	1.24 (0.93-1.66)	0.13
Preterm delivery	2,436 (3.2)	1.0/1.0	699 (3.2)	0.97 (0.89-1.06)	0.95 (0.87-1.04)	276 (3.2)	0.99 (0.87-1.13)	0.93 (0.82-1.06)	0.01

Discussion

This is the first national birth registry-based study to describe the prevalence of anemia in pregnant women in Georgia and evaluate its association with selected adverse maternal outcomes. According to Hb measurements in the GBR, 40.6% of pregnant women in Georgia who delivered between January 1, 2019, and August 31, 2022, had anemia at least once during their pregnancy. Adjara in Western Georgia had the highest prevalence of women with anemia (47.0%), whereas Samtskhe-Javakheti in the south had the lowest prevalence (25.1%). Our results suggest that the overall prevalence of anemia during pregnancy is slightly higher than the global estimate of anemia in pregnant women (36.5%) in 2019 provided by World Bank Health Nutrition and Population Statistics [33]. Moreover, the same source indicated that the prevalence in Georgia is higher than those of neighboring countries, Armenia (18.1%) and Azerbaijan (35%). According to the 2019 WHO Global Health Observatory Data Repository, the prevalence of anemia in pregnant women in Georgia is higher than the average prevalence for upper-middle-income countries in Europe (24.5%) and substantially higher than those of high-income countries (17.2%) [34]. There is a considerable difference in the prevalence of anemia between the regions of Georgia. Accordingly, the presented prevalence for Adjara (47.0%), Kvemo Kartli (46.5%), Imereti (44.1%) and Guria (42.6%) are close to the anemia prevalence in low-income countries (42.6%) whereas the anemia prevalence in Samtskhe-Javakheti (25.1%) is closer to the prevalence in WHO European region (23.5%) [33, 34]. Specific dietary practices and differences in nutrition are possible explanations for the observed regional differences. For instance, in Western Georgia, red meat is less commonly consumed compared to the other parts of the country; this can partly explain the substantially higher prevalence of anemia in Adjara and Imereti than in Samtskhe-Javakheti.

The proportion of women with mild (28.3%), moderate (11.9%), and severe (0.5%) anemia in Georgia was consistent with pooled estimates from Canada and China [8, 9, 12, 18], and lower than that the reported values for some African and Asian countries, such as Somalia, India, and

Pakistan [10, 35]. The low prevalence of severe anemia suggests that implemented national public health measures for anemia prevention, such as free screening and treatment among pregnant women, are efficient. Women with anemia were also more likely to have more than eight ANC visits than women without anemia, indicating that women who have been screened and diagnosed with anemia receive more intense follow-up and treatment than others, which might have resulted in the low observed prevalence of severe anemia.

Another important finding of this study is that 18.1% of all pregnant women who visited the ANC had no reliable Hb measurement during their entire pregnancy, and this proportion varied considerably across the country (Supplementary Table2). This may impact statistics on the true prevalence of anemia in the country and in certain regions. According to the State Antenatal Care Guidelines, all pregnant women attending ANC should have at least one Hb measurement [27]. Hence, the above proportion of women without Hb measurements indicates that despite state-supported ANC and free access to medication for the treatment of iron deficiency anemia during pregnancy (if detected before GA week 13), almost one-fifth of all pregnant women may not receive the care they require or if they do, it may not be registered in the GBR, although this registration is mandatory for ANC providers. These findings suggest that a major priority for Georgian decisionmakers should be to identify the reasons behind the lack of Hb measurements, resolve problems with the registration of implausible values, and follow up women with no Hb measurements to ensure equal access to high-quality ANC for all pregnant women across the country.

Consistent with previous reports, this registry-based study demonstrated an association between anemia during the third trimester and increased odds of admission to the post-delivery ICU [9, 35], although this was not statistically significant using a 5% threshold (*P* for trend = .13). Anemia in pregnancy is a well-known risk factor for post-partum hemorrhage [11], which leads to post-delivery ICU admission. Our results should be interpreted with caution but are notable since hemorrhage has been identified as the leading direct cause of post-delivery ICU admission in Georgia, eventually leading to maternal death [25]. Timely and properly initiated preventive interventions are required during ANC to reduce the risk of maternal morbidity and mortality in Georgia, especially since the maternal mortality rate has increased since 2020 [23].

In contrast to previous studies [3, 8, 10, 35, 36], we found no increased odds for preterm delivery among mothers with anemia in the third trimester, and this is a good message for decisionmakers of the Georgian national healthcare. In fact, we observed an inverse linear trend, suggesting that women with anemia have lower odds of preterm delivery than women without anemia (*P* for trend =0.01). This seems contradictory because several other studies have reported an increased risk of preterm delivery [2, 4]. However, the risk seems to differ according to trimester and across studies; for example, a systematic review and meta-analysis from South Africa, published in 2022 highlights difficulties in clarifying the association between anemia and preterm delivery and in which direction the association might be [12]. Similarly, meta-analyses published in 2000 [37] and 2019 [7] reported a non-significant inverse relationship between anemia in late pregnancy and preterm delivery, which is in accordance with our results. One possible explanation for this difference could be that women in middle-income countries with a well-developed registration system receive intensive follow-up and treatment if they are diagnosed with anemia, while women in lower-income countries with limited capacities in the healthcare sector may not receive optimal follow-up and medical care due to a lack of resources or different screening approaches [8]. Our results show a higher frequency of ANC in pregnant women with a low Hb value. Thus, with special care and treatment, anemia-related preterm delivery is an avoidable adverse maternal outcome, and anemia could be effectively managed even during the third trimester of pregnancy.

The substantial differences in the regional prevalence of anemia in Georgia highlight the need for a customized and stronger public health response and policy implementation toward anemia as a significant public health challenge in Georgia. The proportions of pregnant women who do not attend ANC and of those with no registered Hb values indicate the need for a coordinated strategy to ensure that women in Georgia have equal access and receive optimal care independent of their place of residence. Moreover, it is advisable to evaluate the registration structure of service-related information in the GBR. Nevertheless, focusing on increased, countrywide coverage of the state ANC program with all its features, better access to optimal ANC, and coordinated customized, multilevel responses against anemia are important steps toward mitigating the consequences of maternal anemia and equalizing regional disparities in anemia prevalence.

Strength and limitations

The strength of this study is the large number of women we included, which makes the study representative of pregnant women in Georgia. However, almost one-fifth of the women did not have a valid Hb measurement. Women who do not attend ANC may have a higher risk of anemia because they do not receive proper follow-up from medical personnel. The significant number of pregnant women not attending ANC may have affected the prevalence estimate in the present study. Consequently, there is a need to improve ANC operations to obtain reliable estimates of the prevalence of anemia in pregnant women in Georgia. Based on the GBR data, most women underwent more than one Hb measurement. However, we classified the women according to the lowest registered Hb value and did not consider whether the women were treated or whether the Hb level of those who were treated normalized. This is a limitation of the study. In addition, anemia was identified using measured Hb values, and we could not specify the type of anemia. Moreover, despite controlling for many covariates in the multivariate-adjusted regression analyses, measurement errors could have resulted in residual confounding, and we had no information about several important factors, especially comorbidities such as chronic kidney disease, infections, and cancer, which could have influenced the results.

Despite these limitations, this study provides important insight into the prevalence and potential consequences of anemia in pregnant women in Georgia.

Conclusion

Approximately one-third of pregnant women in Georgia experience anemia at any time during pregnancy, but severe anemia is rare. One-fifth of the women who attended ANC did not have any valid Hb measurement, which is surprising and worrisome since Hb measurements are covered by the state of Georgia. There were large regional differences in the prevalence of anemia, which warrant further investigation. To accelerate progress toward sustainable development goals and decrease the public health burden of anemia in Georgia, early identification and adequate management of anemia during pregnancy are crucial.

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Author contribution

All authors contributed to the methodology, analysis, writing, and editing of the manuscript. All authors approved the final version of the manuscript and agreed to be responsible for all provided information. CR, TM, TB, EA and AG supervised the study. NS, CR, and TM summarized the national datasets and contributed to data collection and curation. NS drafted the manuscript and amended it according to feedback from all authors.

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publication

Not applicable.

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Availability of data and materials

According to Georgian legislation, data from central health registries can be used for research purposes as long as personal data is not shared. Data collected for this study are not publicly available because they contain personalized and potentially identifying information. Proper ethical and legal approvals are required for access before requesting the data, and only anonymous/pseudonymized data can be shared. Researchers can contact the National Center for Disease Control and Public Health in Georgia (ncdc@ncdc.ge) or the corresponding author (natia.skhvitaridze@uit.no) for assistance on how to apply for access to data from registry.

Supporting information

Figure 1.

Figure 2.

S1 File.

S2 File.

S1 Table.

S2 Table.

S3 Table.