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Perinatal mortality and its association with antenatal care utilization in the Republic of Georgia

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Abbreviations

ANC	antenatal care
AOR	adjusted odds ratio
APNCU	adequacy of prenatal care utilisation
CI	confidence interval
CTP	content and timing of care in pregnancy
DAG	directed acyclic graph
END	early neonatal death
GA	gestational age
GBR	Georgian Birth Registry
GEL	Georgian lari
Geostat	National Statistics Office of Georgia
ICD-10	International Classification of Diseases, Revision 10
MDGs	millennium development goals
MoH	Ministry of internally displaced persons from the occupied territories, labour, health and social affairs of Georgia
NCDC	National Centre for Disease Control and Public Health
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
PM	perinatal mortality
SDGs	sustainable development goals

SGA	small for gestational age
UHC	universal health coverage
VRS	Vital Registration System
WHO	World Health Organisation

Short definitions

Early neonatal mortality	death of a livebirth during the first 7 days of life
Infant mortality	death of an infant before the age of 1 year
Late neonatal mortality	death of a livebirth between 8 and 28 completed days of life
Neonatal mortality	death of a livebirth before 28 completed days of life
Perinatal mortality	death of a fetus/livebirth between 22 completed weeks of gestation and the first 7 days of life
Stillbirth	delivery of a fetus which shows no sign of life after 22 completed weeks of gestation
Under-5 mortality	death of a child before the age of 5 years

This thesis is based on the following papers

I. Manjavidze T, Rylander C, Skjeldestad FE, Kazakhashvili N, Anda EE. Incidence and Causes of Perinatal Mortality in Georgia. J Epidemiol Glob Health. 2019;9:163-168. doi:10.2991/jegh.k.190818.001

II. Manjavidze T, Rylander C, Skjeldestad FE, Kazakhashvili N, Anda EE. Unattended Pregnancies and Perinatal Mortality in Georgia. Risk Manag Healthc Policy. 2020;13:313-321. https://doi.org/10.2147/RMHP.S243207

III. Manjavidze T, Rylander C, Skjeldestad FE, Kazakhashvili N, Anda EE. The Impact of Antenatal Care Utilization on Perinatal Mortality and Admission to Neonatal Intensive Care Units in Georgia. PLOS ONE. Submitted.

Abstract

Background: Despite recent achievements, perinatal mortality (PM) rates remain high worldwide, especially in low-income countries (>30 per 1000 births). PM is defined as the death of a fetus/livebirth between 22 completed weeks of gestation and the first 7 days of life. Simple, non-invasive interventions could reduce PM rates, since most deaths are caused by preventable conditions. Adequate antenatal care (ANC) is one of the steps towards better pregnancy outcomes. Georgia has one of the highest PM rates in Europe, but they also have high ANC coverage. We aimed to understand the causes of PM and the impact of ANC on PM in the Republic of Georgia.

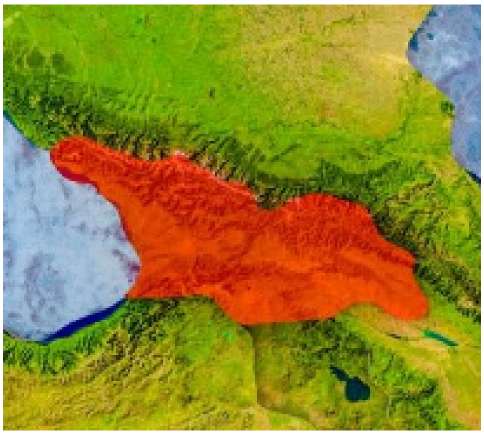
Methods: The Georgian Birth Registry was the main source of data, and the Vital Registration System was used as a supplementary source for data validation. Mothers who delivered in 2017-2019 and their newborn were included in the analysis. We used the Wigglesworth classification to categorise causes of death, and the adequacy of prenatal care utilisation index to analyse ANC. We assessed potential confounders by directed acyclic graphs and detected associations between exposures and outcomes by logistic regression analyses.

Results: The majority of stillbirths in Georgia were reported as unexplained (80%) and antepartum (85%), and preterm birth complications and congenital malformations were the most common causes of early neonatal death (END). The stillbirth to END ratio was 2.1, and newborn who died during first day of life represented 30% of the total number of ENDs. Unattended pregnancies (no ANC attendance) comprised 5.6% of all pregnancies in our study and carried more than two times higher odds of PM compared to attended pregnancies. Sixty-two percent of women did not receive adequate care during the study period. Women in the inadequate care group had the highest odds of PM when using the adequate care group as a reference; women who received intermediate care had the lowest odds of PM.

Conclusion: Initially, our study revealed potential misclassification between stillbirths and ENDs. We suspect that asphyxiated newborn who died shortly after birth might be classified as antepartum stillbirths. Adequate ANC has the potential to reduce PM and should be used as a tool for improving newborn health outcomes. Further, some women without any particular medical need may receive more than the recommended number of ANC visits. Increasing the number of ANC visits from four to eight did not seem to improve PM rates. Therefore, it is not sufficient to look only at the number of ANC visits; the quality should also be monitored.

PhD timeline
Perinatal mortality and its association with antenatal care utilization in the Republic of Georgia

Birth registry in Georgia



In order to address issues related to maternal and newborn health, Georgia implemented the Georgian Birth Registry (GBR) in 2016. GBR data were 99.8% in accordance with official numbers in 2019.

Paper I

Published in the Journal of epidemiology and global health

Incidende and causes of perinatal mortality in Georgia

Paper II

Published in Risk management and healthcare policy

Unattended pregnancies and perinatal mortality in Georgia

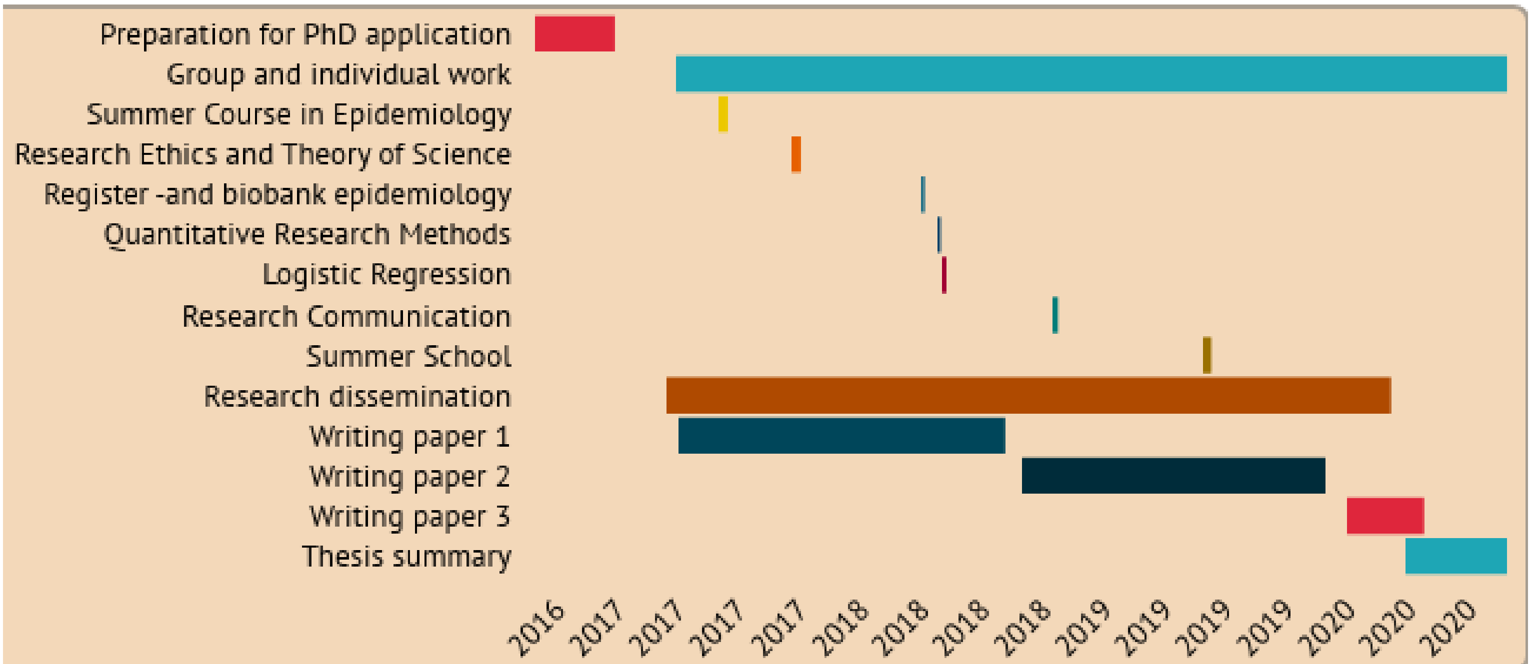
Paper III

Submitted to PLOS ONE

The impact of antenatal care utilization on perinatal mortality and admission to neonatal intensive care units in Georgia

PhD project

I received a 3-year PhD position, funded by DIKU (Norwegian Agency for International Cooperation and Quality Enhancement in Higher Education), and started working on perinatal mortality (PM) in Georgia, which has one of the highest PM rates in Europe. The aim of the PhD project was to identify the causes and factors associated with this high PM rate. Specifically, we assessed the impact of antenatal care on PM. Due to the the COVID-19 pandemic, a 6 month time extension was granted



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1 Introduction

Healthy newborn is a marker of a healthy society, and the neonatal mortality rate strongly reflects the overall effectiveness of a healthcare system. Thus, ending preventable newborn deaths is part of the United Nation's sustainable development goals (SDGs), which have been adopted by most countries (1-3). The world has made significant progress in reducing under-5 mortality; however, more than five million under-5 deaths still occur annually, with widespread regional differences (4). Within the framework of the United Nation's millennium development goals (MDGs), under-5 mortality was reduced by 43% between 2000 and 2015. The absolute majority (98%) of under-5 and neonatal mortality cases occur in low-income countries, where resources are limited (4) (Figure 1). At the same time, most causes of death are preventable by simple, non-invasive interventions, for example, antenatal care (ANC, i.e., care during pregnancy), postpartum care, delivery managed by a skilled healthcare provider, and kangaroo mother care.

The Republic of Georgia is a developing, upper-middle-income country with a relatively high PM rate compared to Europe. With the aim to create a data source that contains individual-level information to help address maternal and newborn health conditions, the country implemented the Georgian Birth Registry (GBR) in 2016 as a means to understand country-specific modifiable factors that contribute to pregnancy and delivery complications. ANC is considered one of the strongest short-term factors that can be modified to improve pregnancy outcomes.

The delivery of a fetus with no sign of life after 22 completed weeks of gestation is known as a stillbirth; the death of a livebirth during the first 7 days (168 hours) of life is called early neonatal death (END). Stillbirths and ENDs together comprise perinatal mortality (PM), and their causes are interlinked. This thesis aimed to identify the main causes of PM and the impact of ANC on PM in Georgia.

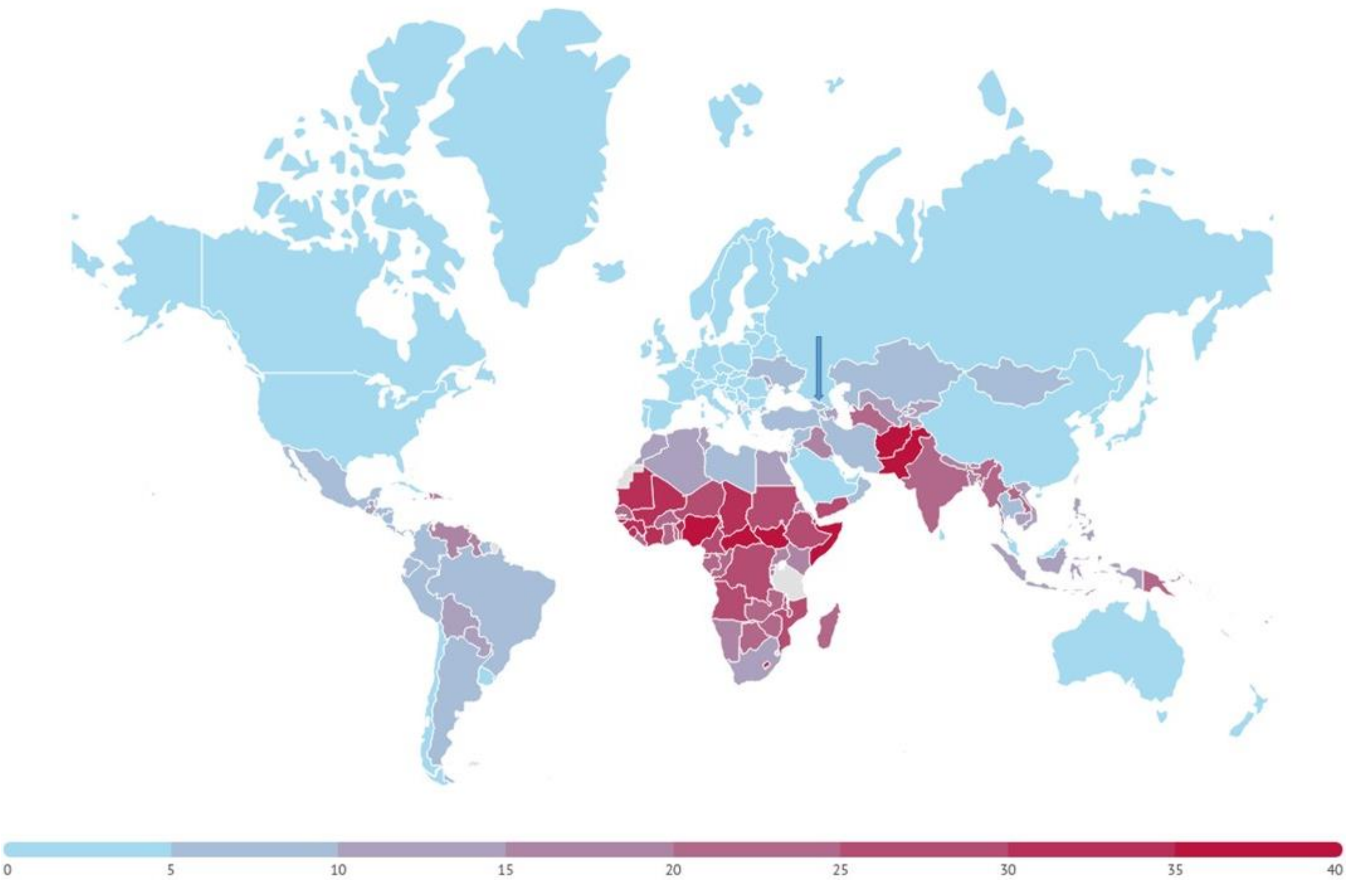

Figure 1. Neonatal mortality rate per 1000 livebirths by country, 2018. Created using Infogram software.

1.1 Global perinatal mortality rates

In 2015, the worldwide neonatal mortality rate was 19.1 per 1000 births, and the under-5 mortality rate was 42.4 per 1000 births. Reducing neonatal mortality to 12 per 1000 livebirths and under-5 mortality to 25 per 1000 livebirths by 2030 is one of the United Nation's SDGs (1). Under-5 mortality decreased by 46% between 2000 and 2018. Despite this success, almost half of under-5 deaths (47% in 2018) still occur during the neonatal period, i.e., before 28 completed days of life (4). Of these, 75% die during the early neonatal period, i.e., during the first 7 days of life, thus are counted as PM deaths (5). Globally, around 2.5 million die annually during the neonatal period, and of those, one million die within the first day. No other day in a human's life span carries a higher risk of mortality than that first day of life (5, 6). Additionally, 2.8 million stillbirths occur every year, also counted as PM deaths, and the absolute majority of those (98%) take place in the least developed countries. PM rates differ considerably across regions and countries (5, 7-9), ranging from 40 per 1000 births in Nigeria, Western Africa to 3-5 per 1000 births in the Nordic countries in Northen Europe. This highlights the potential to reduce preventable deaths. The risk factors for and causes of PM differ from those of under-5 mortality in that most of the PM causes are preventable which, in turn, leaves room for improvement (4).

1.1.1 Stillbirth rate worldwide

For some reason, reducing preventable stillbirths has been neglected in the global agenda and is mostly unrecognised in relevant global policies (10, 11), even though the risk factors for stillbirths are often the same as for ENDs. While the burden of stillbirths is large, simple non-invasive interventions can reduce the rates significantly, especially in low-income countries (10). Counting all stillbirths is a challenge for low- and middle-income countries, due to weak vital registration systems and underreporting. The first step to preventing any condition, disease, or death, is to estimate its burden. Therefore, achieving the ambitious target of ending preventable stillbirth is complicated by registration difficulties. Stillbirth rates range from 2.0 per 1000 births in Finland to 40.0 per 1000 births in Nigeria and Pakistan (11). These figures demonstrate the potential to reduce stillbirths in countries with high burdens.

1.1.1.1 Stillbirth – time of death

Timing of fetal death is very important. Intrapartum stillbirth is recognised as the death of a fetus after the onset of labour but before delivery. Assessment of intrapartum stillbirth is based on heartbeat monitoring during labour, or, if such monitoring is not possible, signs of skin maceration. The intrapartum stillbirth rate is an important marker of quality of care, support during labour, and access to medical facilities at the onset of labour (12). Intrapartum stillbirth comprises one-third of all stillbirths and is considered to be avoidable with better obstetric care (13). On the other hand, antepartum stillbirth, i.e., fetal death before the onset of labour, is largely avoidable if high-quality ANC is provided (14). Disparities between stillbirth rates and time of death are partially linked to ANC and whether the delivery was managed by a skilled healthcare provider (11).

1.1.2 Early neonatal mortality rates worldwide

An estimated two million ENDs occur every year (5). Between 61% and 85% of neonatal deaths in European countries are ENDs (15). The worldwide END rate is decreasing; but the share of under-5 mortality is larger than before (5). END rates in Europe vary from 1.0 per 1000 livebirths in Iceland, Finland, and the Czech Republic, to 3.7 per 1000 livebirths in Bulgaria based on the latest Euro-Peristat project data (16). More than half of ENDs occur during the first day of life (6, 17), and this proportion is consistent across countries with different mortality rates (6).

1.2 The causes of perinatal mortality

Around 40% of all stillbirths worldwide have an undetermined cause of death. The proportion of unexplained stillbirth is higher in low-income countries than in the rest of the world (18, 19). Despite their manageable and avoidable nature, infection and hypoxia are the most common causes of stillbirth in low- and middle-income countries. On the contrary, in high-income countries, antepartum haemorrhage and congenital malformations are the most common causes of stillbirth (20). Preterm birth complications, congenital malformations, and birth asphyxia (intrapartum-related events) are considered the most common causes of END (5, 18, 21). The diversity of causes of PM across countries shows gaps in the care provided in limited-resource settings.

The considerable differences in causes of PM across countries highlights the inequality in care before and during pregnancy and labour. Moreover, intrapartum stillbirth and newborn death within the first hours of life are largely preventable through better care during labour, and they usually have similar intrapartum-related causes.

1.3 Thresholds for defining perinatal mortality

The gestational age (GA) threshold for distinguishing between PM and spontaneous abortion varies across countries, and the criteria for distinction between these two conditions are not uniformly accepted (22, 23). Although the International Classification of Diseases Revision 10 (ICD-10) suggests using a birthweight of 500 grams as a threshold for registering stillbirth, or a GA of 22 completed weeks if birthweight is not known, GA is accepted as a better predictor of maturity in most countries with comprehensive registration systems (12). In Europe, the GA threshold for stillbirth varies from a GA of 16 weeks (in Norway) to 24 weeks (in the United Kingdom), whereas stillbirths are only counted after a GA of 28 completed weeks in countries with limited resources. The GA threshold in the ICD-10 was reduced from 28 to 22 weeks following the increased possibility of saving extremely preterm newborn (12).

1.4 Prevention of perinatal mortality

ANC and postpartum care, in addition to labour and delivery management by skilled health care providers, can potentially prevent one-third of stillbirths and two-thirds of neonatal deaths (24). Cost-effective and simple interventions like cord cleaning with chlorhexidine, kangaroo mother care, antenatal steroids, treatment of neonatal infections, resuscitation, and continuous positive airway pressure can improve outcomes of preterm and small-for-gestational age (SGA) newborn (3). Preterm deliveries and SGA newborn are the most important indirect causes of neonatal death (80%) (25). Despite increased coverage of evidence-based interventions in some areas, health care structures in low- and middle-income countries are inadequate to implement these interventions (24).

1.5 Antenatal care and perinatal mortality

The Beijing declaration and platform for action adopted in 1995 by the United Nation's Fourth World Congress as an agenda for women's empowerment states that every woman should have the right and access to appropriate healthcare services that will enable a safe pregnancy and delivery, and provide couples with the best chance of having a healthy infant (26). Therefore, governments should promote proper care during pregnancy as a fundamental human right.

ANC is routine care of pregnant women provided between conception and the onset of labour. It is defined as 'the care provided by skilled healthcare professionals to pregnant women and adolescent girls in order to ensure the best health conditions for both mother and baby during pregnancy. The components of ANC include: risk identification; prevention and management of pregnancy-related or concurrent diseases; and health education and health promotion' (27). The history of research on ANC and its impact on pregnancy outcomes started at the end of the 19th century, when J.W. Ballantyne noted and discussed the significance of ANC (28, 29). Since 2000, research has provided convincing results that timely, adequate, and appropriate ANC can reduce the risk of adverse pregnancy outcomes, such as maternal mortality and PM, pregnancy and postpartum complications, preterm birth, and SGA newborn (24, 30-40). Effective communication, educating pregnant woman, and psychological support are additional benefits of proper ANC (27). Suboptimal care during pregnancy is one explanation for the substantial differences in PM across countries (34). Many lives could be saved if effective interventions, such as ANC, were implemented and provided in a routine, timely manner by trained healthcare providers (41).

1.6 Recommendations for antenatal care

In 2001, the World Health Organisation (WHO) recommended a minimum of four ANC visits for women with a healthy, low-risk pregnancy (42, 43). Fifteen years later, this recommendation changed to eight ANC visits, following a Cochrane review that included seven randomised controlled trials and suggested an increased risk of PM among women with reduced ANC visits when compared to those who received standard care (i.e., at least eight ANC visits) (44). Further, PM was shown to be increased among women with reduced ANC visits in low- and middle-income countries, but not those in high-income countries (44).

The latest WHO guidance on ANC advises that countries make efforts in several areas, like maternal and fetal assessments, preventive measures, and educational and physiological support (27). The guidelines of the National Institute for Health and Care Excellence (NICE) in the United Kingdom suggest a schedule of 10 ANC visits for nulliparous and seven ANC visits for multiparous women with a low-risk pregnancy (45). NICE guidelines are accepted in the United Kingdom and Australia, and they state that, ideally, pregnant women should initiate ANC by 10 weeks of pregnancy (46, 47). The number of ANC visits provided is based on an assessment of individual needs and should take into account parity, current mental and medical conditions, and previous pregnancy complications and outcomes (i.e., obstetric history) (45).

WHO and NICE guidelines on ANC are designed to be adaptable, so that each country can modify and implement these recommendations based on their respective economic, social, and medical situation. All these derive from the burdens of disease, the overall healthcare system, access to medical services, cultural behaviour, and many other factors. Early ANC initiation provides an opportunity to screen for sexually transmitted diseases, congenital malformations, and genetic disorders; to assess GA; to treat preterm labour; and to prescribe supplements meant to reduce pregnancy and delivery complications (37). The WHO recommends that all pregnant women initiate ANC before 12 weeks of pregnancy in order to improve safety during pregnancy and increase the possibility of detecting maternal and fetal problems (27).

1.7 The role of registries in perinatal epidemiology

The history of medical birth registries started in Norway in 1967. The thalidomide catastrophe formed the idea that a registry system could help discover other similar problems in advance (48). Originally, the aim was simply to survey birth defects, but today the use is much wider (49). Since then, Denmark (1968), Iceland (1972), Sweden (1973), and Finland (1987) have established medical birth registries with diverse contexts and information, but they had a common goal – to collect information about pregnant women and newborn to better understand factors influencing maternal and child health. The information collected in medical birth registries became a tool for clinical and epidemiological research. Data from Nordic registries, in combination with biobanks, have been widely used to analyse factors affecting pregnancy (50). One such example is the Norwegian mother, father, and child cohort study, which was implemented to investigate the causal impact of conditions during pregnancy on child development. Currently, most European countries have established national medical birth registries for the same purposes, and comprehensive research based on these registries has been conducted to identify factors that may affect PM (51-54).

Registries collect systematic, longitudinal, and uniform information on health determinants and outcomes, with the aim to support health surveillance and clinical decision-making, and to improve scientific knowledge (55). The collection of primary data on maternal and child health starts with the recording of the pregnancy at the first ANC visit. Information on maternal and fetal health, maternal characteristics, and the services women receive are added throughout the pregnancy (55).

The Euro-Peristat project monitors perinatal health indicators in Europe using registry data from 31 European countries. As stated in the project summary in 2015, the completeness and coverage of birth registries, in combination with data from vital registration systems, are usually close to 100%, even in countries where it is not mandatory to provide data to registries (16).

Birth registry-based studies on associations between early life exposures, exposures during pregnancy, and the perinatal outcomes of disease prevention and positive pregnancy experience are frequently published. Maternal characteristics like body mass index, age, parity, and delivery type, as well as newborn characteristics like birthweight, have been studied as factors that might affect PM (56-61). Registries are increasingly important, and research possibilities, data provision, and data collection are routinely and continuously managed, as they are directly applicable to epidemiological analyses of patterns of diseases using long-term data.

Electronic health records and medical registries are also important in the clinical decision-making process, as they can help improve health outcomes through proper follow-up. They can also improve the exchange of information between providers, risk identification, comprehensive research, and the building of scientific evidence (62).

1.8 The Republic of Georgia, საქართველო (Sak’art’velo)

The Republic of Georgia is an upper-middle income country located in the Caucasus region, between Europe and Central Asia, bordering the Black Sea to the west. The neighbouring countries are Turkey and Armenia to the south, Azerbaijan to the southeast, and Russia to the north.

Georgia made considerable progress after its independence from the Soviet Union in 1991. However, the population has decreased by around 30%, due to an increasing rate of out-migration and Russian occupation of Abkhazia (1991) and South Ossetia (2008). The population has increased slightly since 2013. The Georgian healthcare system is decentralised and almost all medical facilities are private. Since 2012, the government has provided universal health coverage (UHC) to all Georgian citizens who do not have private insurance. Households living below the poverty level, children under the age of 5 years, and retired persons, have more advantages under the UHC in terms of financial and medical support (63).

Since obtaining its independence, the number of people living below the poverty level and unemployment rates have decreased, and economic growth and the gross domestic product have increased; however, Georgia still faces difficulties related to the economic transition. The decrease in maternal, child, and premature mortality has been significant: life expectancy at birth increased from 70.0 in 2000 to 74.0 years in 2018 (64). Georgia achieved the fourth MDG and reduced its under-5 mortality rate more than two-thirds from 2000 to 2013 (65). Nevertheless, great efforts are still necessary if Georgia is to achieve the targets it has set for itself within the framework of the SDGs, since it is following the recommendations and standards set by the WHO and the European Union.

Figure 2. Map of the Republic of Georgia including national regions. Created using Infogram software.

1.8.1 Population characteristics in Georgia

The total population in Georgia in 2020 is 3.72 million. The country is divided into eleven regions (Figure 2), including the capital and largest city, Tbilisi, which has 1.19 million inhabitants. The majority (59%) of the population live in urban areas. The unemployment rate is 12.7%, and more than half of employed people are self-employed. The latest census data showed that 86.8% of the Georgian population are native Georgians; the largest ethnic minorities are Azerbaijanis (6.3%) and Armenians (4.5%) (66). Life expectancy at birth 69.7 for males and 78.2 for females.

The crude birth rate was increasing slightly until 2008, when it began to fluctuate. In 2018, the birth rate was 13.7 per 100 000 population, which was down from 16.3 in 2014; the death rate has also been decreasing slightly (Figure 3). Based on the annual report of the National Statistics Office of Georgia (Geostat), the leading causes of death in Georgia are cardiovascular disease (46%) and cancer (17%) (67). The mean age of women at first childbirth increased from 25.5 in 2008 to 27.8 in 2018. In 2018, 44.6% of newborn were born by caesarean section, which represents one of the highest caesarean section rates in the world. The abortion rate is also high at 444.5 per 1000 livebirths (64). Similar to the birth rate, the total fertility rate decreased slightly, from 2.3 in 2015 to 2.1 in 2018.

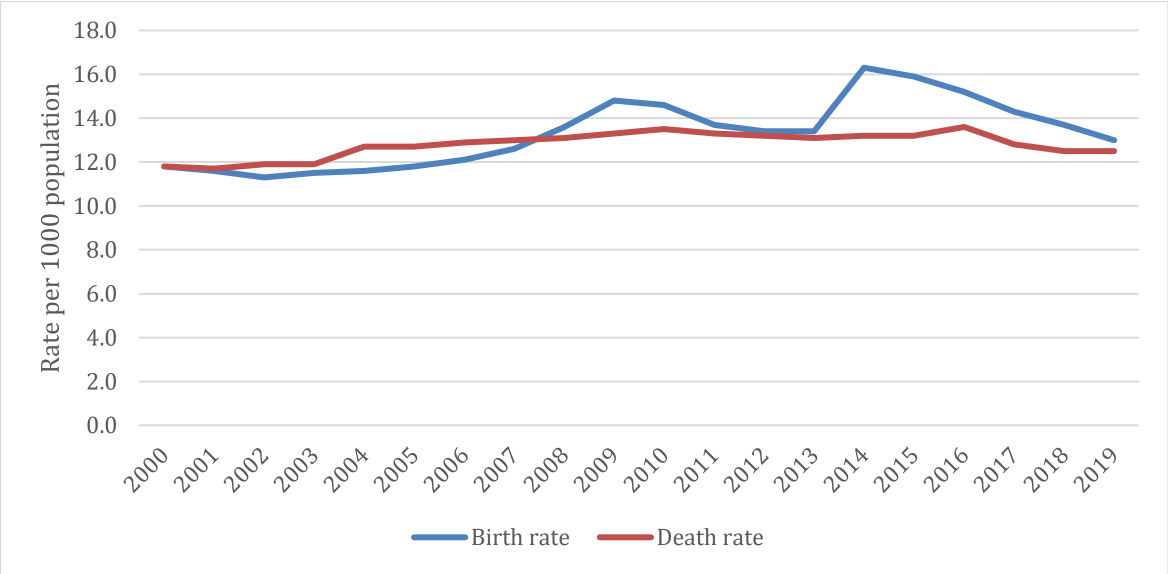

Figure 3. Crude birth and death rates* in Georgia, 2000-2019.

*The rates are reported by National Statistics Office. The registration of births and deaths till 2014 are based on the retro-projection (estimated number), starting from 2014 based on the registered data.

1.8.2 Perinatal mortality in Georgia

The PM rate in Georgia decreased by more than 40% between 2009 (19.7 per 1000 births) and 2018 (11.7 per 1000 births), but then stagnated, and remains one of the highest rates in Europe (7). In 2017, the PM rate was 13.8, and this rate decreased slightly in 2018. Based on official statistics, stillbirth and END rates also decreased from 9.4 and 4.5 per 1000 births, respectively, in 2017 to 8.5 and 3.2 in 2018. Georgian guidelines are in line with internationally accepted definitions of stillbirth and END, i.e., the delivery of a fetus which shows no signs of life after a GA of 22 completed weeks and the death of a livebirth during the first 7 days (168 hours) of life, respectively.

The Georgian government approved a national strategy for supporting maternal and newborn health from 2017 to 2030 as a main long-term action plan (68). The document is harmonised with international strategic documents, including the United Nation's MDGs (2015), WHO Health 2020: the European policy for health and wellbeing (2012), and the WHO Action plan for sexual and reproductive health. The document states that, despite improvements in the field of maternal and child healthcare in recent decades, Georgia still faces challenges in fulfilling its targets and aims, which are to reduce its PM rate to 8.0 per 1000 births, its stillbirth rate to 6.8 per 1000 births, and its END rate to 3.0 per 1000 livebirths by 2030.

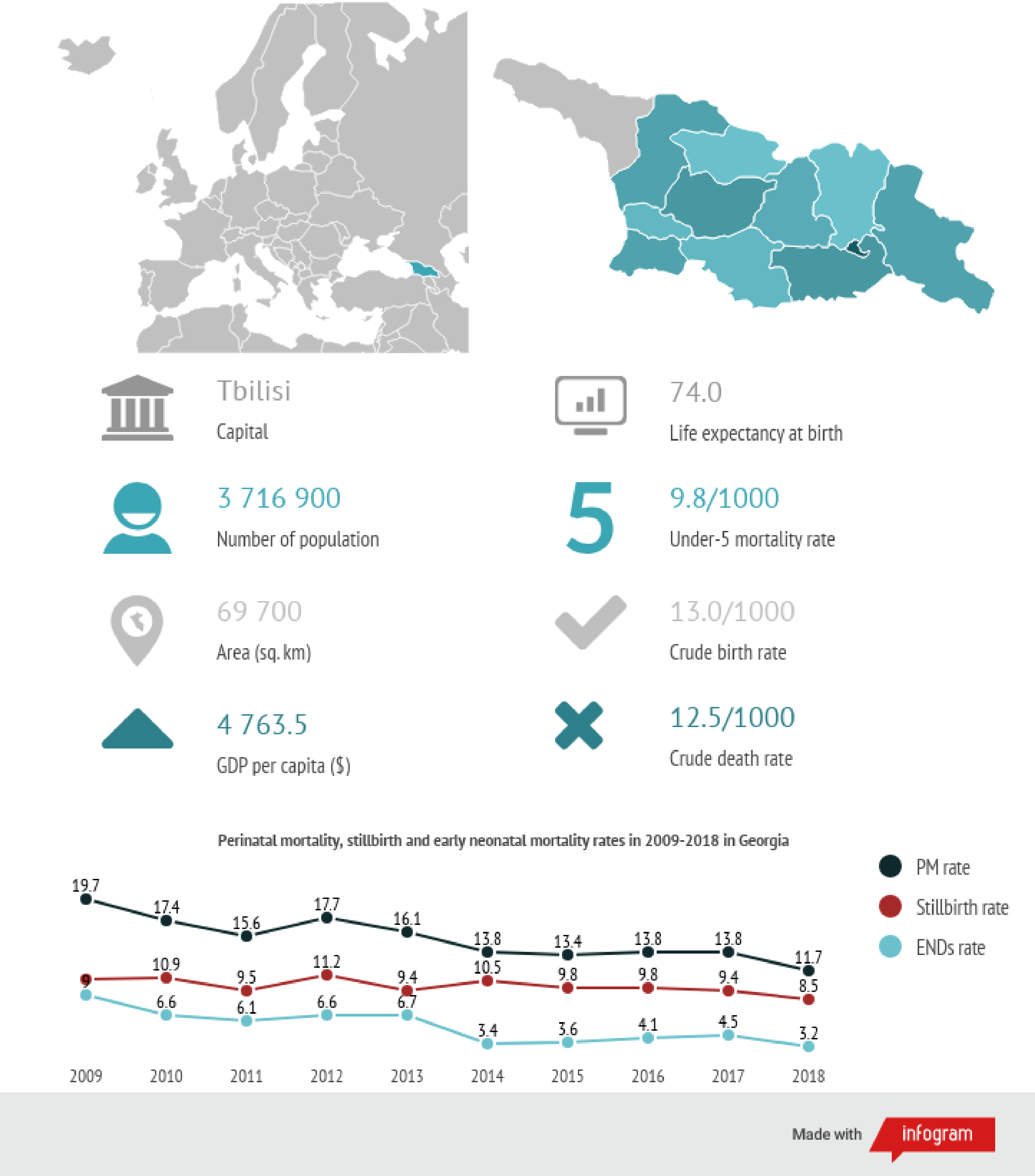

Figure 4. Infographic about Georgia (საქართველო, Sak'art'velo). Created using Infogram software. Data source: Annual statistical yearbook, NCDC, 2018.

1.8.3 Access to healthcare for pregnant women in Georgia

The number of doctors in Georgia is high, and the ratio of nurses to doctors (0.6) is much lower than in many European Union countries (2.0-2.7) (64, 69). More than 270 hospitals and 2200 primary healthcare centres are operating in the country. In addition to UHC, the Georgian government provides financial assistance to pregnant women and newborn through the 'Maternal and Child Health State Programme', which finances ANC (through the ANC programme) and screening tests for hepatitis C and B viruses, HIV, and syphilis for pregnant women. The programme also finances routine screening tests for hearing impairment, phenylketonuria, cystic fibrosis, hypothyroidism, and hyperphenylalaninemia in newborn. Before 1 February 2018, the ANC programme covered four ANC visits ('old' ANC programme) for every pregnant woman who initiated care before 12 completed weeks of pregnancy. Since 1 February 2018, the programme has covered eight ANC visits ('new' ANC programme) for every pregnant woman who initiates care before 12 completed weeks of pregnancy. The government covers costs up to 500 Georgian lari (GEL) for a vaginal delivery and up to 800 GEL for a caesarean section. Any costs that exceed this threshold would be considered a private responsibility.

The perinatal regionalisation process, initiated in 2015, classified ANC centres and maternity homes into primary care (basic care), secondary care (specialised care), and tertiary care (subspecialised care) centres. This process aimed to ensure that proper, safer, higher-quality antenatal, obstetrical, and neonatal services were provided to pregnant women and their newborn. Perinatal regionalisation has been successfully implemented in other countries and was shown to improve in-service delivery processes (70).

1.8.4 Data collection on perinatal health in Georgia

Geostat is the main institution that produces and disseminates statistical information according to the law. Geostat data on number of births and deaths are derived from the Vital Registration System (VRS), which is under the control of the National Centre for Disease Control and Public Health (NCDC). VRS ensures registration of all births and deaths that occur in the country's territory, and the Ministry of Justice, which also registers births of citizens of Georgia that occur outside the country. Due to this difference in data collection, disparities may occur when comparing the VRS to official Geostat data. Data are entered into the VRS by medical personnel, and the registry serves as a single source for the issuing of birth and death certificates. There is a penalty for delaying or not registering births and deaths; if the case is not registered within 5 working days, the person in charge of the registration process must pay 500 GEL. This ensures that very few births or deaths are missed.

Since 1996, the Department of Medical Statistics at the NCDC has collected information about maternal and child heath from all perinatal healthcare providers monthly and annually. The aggregated data provide information on core medical indicators and are used in official annual statistical reports. From 2013, the Ministry of internally displaced persons from the occupied territories, labour, health and social affairs of Georgia (MoH) implemented an urgent notification system for maternal mortality, under-5 mortality, and stillbirths. Thus, all medical facilities are required to notify the MoH of these cases, by phone and by completing an electronic form, within 24 hours of death. In addition, a copy of the medical records for each case must be delivered to the MoH within 5 days for further evaluation.

In the past, only aggregated data perinatal health indicators from paper-based forms and reproductive health surveys were available, making it difficult to identify underlying causes of adverse pregnancy outcomes, pregnancy complications, or delivery complications. For this reason, the GBR, a medical birth registry, was implemented in 2016 as a national data source for information on individual pregnant women and their newborn.

1.8.5 The Georgian Birth Registry

The GBR was made possible through a successful collaboration between Georgia and Norway, specifically the NCDC, UiT - The Arctic University of Norway, The United Nations Children's Fund (UNICEF), and Consulting & IT innovations, but there were several challenges during the implementation of the GBR. One of the most important was to make it both useful for statistical analysis and for internal use at medical facilities. Before mandatory registration in the GBR began, the registry office of the NCDC conducted more than 200 face-to-face training sessions all over the country for medical personnel who would be responsible for entering data into the registry. In order to ensure that the GBR would function properly, pilot testing was conducted in the two biggest medical facilities in Tbilisi 6 months before launch (second half of 2015). During this period, most technical difficulties and problems were identified and solved.

Following the pilot testing process, the GBR officially launched on 4 January 2016, when the MoH made it mandatory to input information, and the GBR became the first electronic medical birth registry with national coverage in a current low-to-middle-income country (71). Healthcare providers – mostly obstetricians, gynaecologists, and paediatricians, but in some settings also nurses and statisticians – from more than 350 ANC centres and medical facilities imput information on a daily basis using an online platform. All pregnancies at medical facilities are registered in the system as soon as they are identified (i.e., as soon as women visit healthcare facility and perform ultrasound scan), and all medical facility-based deliveries are also registered. The proportion of deliveries managed by skilled healthcare providers in Georgia is 99.9% (the proportion of home deliveries is 0.01% (64)); thus, almost every woman who delivers in Georgia is registered in the GBR, even if she did not have any ANC visits during her pregnancy (64, 71). The GBR contains fully digitalised, uniform, individual-level, real-time, longitudinal data on health-related information like maternal characteristics, previous medical history, and current conditions, which automatically generate from the online platform. Pregnancy complications, delivery complications, and causes of death are classified in the GBR according to the ICD-10. The GBR also contains data on all pregnancy outcomes, including abortions, deliveries, and ectopic pregnancies.

After they are entered, GBR data are organized by the registry office at the NCDC, which handles case validation and assures data completeness and accuracy. The registry office helps reduce the amount of missing, insufficient, or incorrect information and assists medical facilities in providing data that are as precise as possible. Moreover, each month the registry office checks all information registered in the GBR against the VRS and other data sources. There are also several control mechanisms in the software to avoid duplicates, for example birthweight, GA, delivery type, interventions during labour. These mechanisms, in addition to consistent communication with healthcare providers, are increasing the completeness of information year by year. The last 3 years of data from the GBR showed high completeness, with the number of livebirths, stillbirths, and mothers in agreement with those from Geostat and the VBR. The coverage of all births in the GBR was 98% in 2016, and this increased to 99.8% in 2018. When compared with the data from Geostat, the 0.2% difference in coverage was found to be due to differences in registration practices between the two systems. Indeed, the GBR includes all pregnant women who attended at least one ANC visit and/or gave birth in any medical facility in the country, whereas Geostat registers all newborn, including those born outside the country, that need a Georgian identification number, which obviously is not the reason for registration in the GBR.

However, there are several challenges with data completeness and accuracy that can be only identified during research and detailed analyses. A study started in May 2019 aims to validate information in the GBR against its primary source – the medical files. The medical files of 1250 randomly selected women and newborn are being checked by the registry office in order to identify the completeness of GBR data and detect gaps in the system. The validation study is ongoing, thus results are not currently available. Moreover, unlike the number of deliveries, we assume that the number of abortions in the GBR is underreported. Indeed, there is limited possibility to validate data on abortions, since the GBR is the only registry to contain individual-level data, and cross-checking this information with paper-based forms that contain aggregated data is, obviously, imperfect.

Although the initial aim of the GBR was to collect data on pregnancies, births, delivery-related complications, and fetal and newborn conditions, it now carries other responsibilities as well. Firstly, application for and acceptance into the Georgian government's ANC programme is now done through the GBR. Before 2016, pregnant women had to complete a paper ANC voucher at the Social Service Agency, after which they received a paper that confirmed they were a beneficiary of the programme. Secondly, the GBR is now the primary source of information used by the MoH to determine perinatal regionalisation for ANC centres and maternity homes. Regionalisation is determined based on many factors, including available technology and specialisations. Medical facilities must fulfil various requirements to maintain their level, licence, and contracts. The MoH also uses information from the GBR to address issues with hospital performance.

The GBR also has great value for research and scientific knowledge. Master and PhD students alike, use GBR data for their research purposes, which has proven valuable for increasing competence in the field of maternal and child health in Georgia. The GBR has individual-level data available to help in the identification of patterns and causes of maternal mortality and PM. Because Georgia has one of the highest caesarean section rates in the world, a high rate of ANC attendance, and almost 100% of women have deliveries that are managed by skilled healthcare providers in medical facilities, we were interested in determining which factors contributed most to the high PM rate in Georgia, in order to create appropriate modification and prevention strategies.

2 Aim of the thesis

Georgia has lacked information on the causes and underlying factors of PM because comprehensive research on perinatal health has not been conducted. The GBR created new opportunities to study newborn outcomes and their relationship with maternal characteristics and country-specific exposures during pregnancy using prospectively collected data. Thus, we investigated the causes of PM and its association with ANC and modifiable risk factors to add to the scientific knowledge on this topic and avoid preventable newborn deaths.

The aim of the thesis was to classify the causes of PM and assess the impact of modifiable risk factors, like ANC utilisation, on PM in Georgia using data from the GBR. Specifically:

1. To assess the rates and distribution of stillbirths, ENDs and PM and classify the primary causes of PM in Georgia (Paper I),
2. To investigate the association between socio-demographic factors, unattended pregnancies and PM (Paper II),
3. To evaluate the association between ANC utilisation and timing of ANC utilisation, and the odds of admission to the neonatal intensive care unit (NICU) and PM (Paper III).

3 Materials and methods

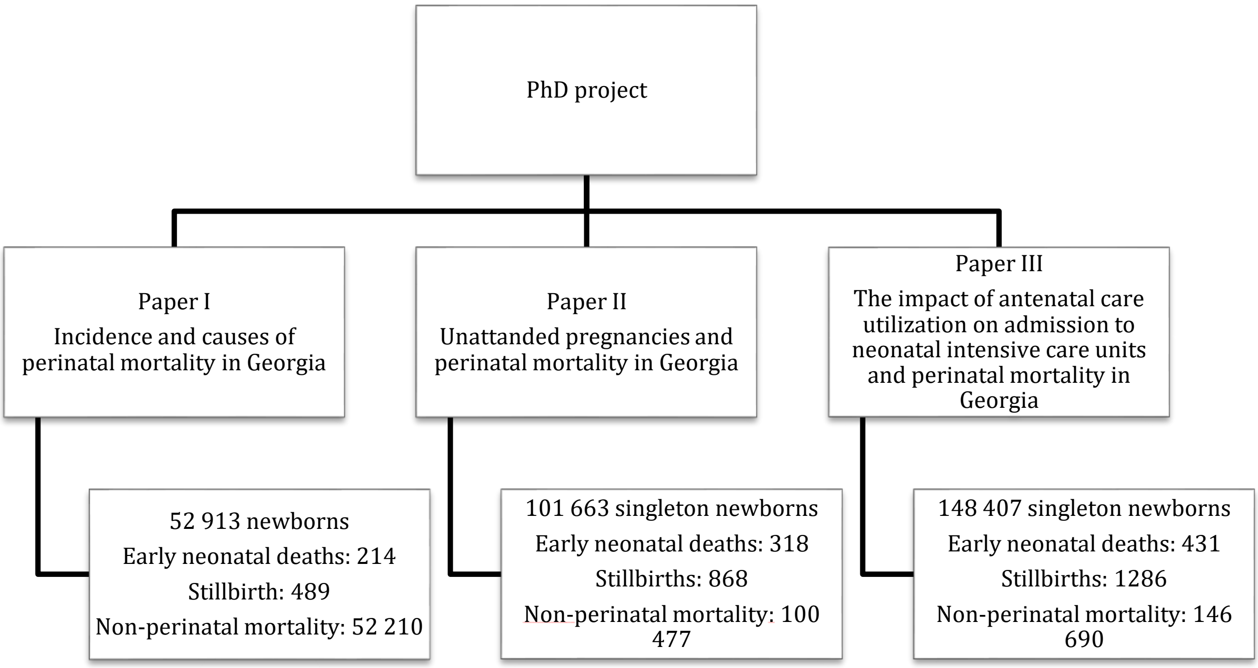

Figure 5. Study samples of Papers I, II, and III of the PhD project.

For the three papers included in this thesis, the newly implemented GBR was the main source of data, in combination with the VRS, which was used as a tool for case validation (stillbirths and ENDs) and for time and cause of death. Additionally, in Paper I, the primary and secondary causes of death from the VRS were used to supplement data from the GBR. The hospitalization registry was used in Paper III to validate NICU admissions.

3.1 Study samples

Paper I

In Paper I, we included all mothers (n=52 228) with medical facility-based deliveries in 2017 registered in the GBR and their newborns (n=52 961). Mothers and newborns with biologically implausible values like parity >15 (n=14), maternal age <13 or >53 years (n=2), GA >43 weeks (n=2), or birthweight <100 g (n=30) were excluded because they were seen as a potential outliers. Additionally, ENDs without any personal identification (n=24) were excluded from the study, since their GBR data could not be linked to the VRS. The final study sample comprised 52 180 mothers and 52 913 newborn. In total, 703 PM cases were included in the analysis; 489 were registered as stillbirths and 214 as ENDs (Figure 5).

Paper II

In Paper II, we included all mothers (n=103 128) with medical facility-based deliveries in 2017 and 2018 registered in the GBR and their newborn (n=104 597). Mothers and newborn with biologically implausible values like parity >15 (n=13), maternal age >53 years (n=8), and GA >43 weeks (n=2) were excluded as plausible outliers. Due to the higher risk of mortality, multiple births (n=2911) were also excluded from the analysis to ensure that unbiased odds of ANC on PM are minimized. The final study population comprised 101 663 singleton newborn and their mothers (Figure 5).

Paper III

In Paper III, we included all mothers (n=150 593) with medical facility-based deliveries from 2017 to 2019 registered in the GBR and their newborn (152 798). Mothers and newborn with biologically implausible values like parity >15 (n=40), GA >43 weeks (n=18), and maternal age >53 years (n=7) were excluded because they were seen as potential outliers. Due to the higher risk of pregnancy complications and delivery complications, multiple births (n=2924) were also excluded. The final study sample comprised 148 407 singleton newborn and their mothers (Figure 5).

3.2 Data sources, included variables and classification of exposures

Paper I

Paper I assessed the incidence and causes of PM in Georgia, thus the following variables were extracted from the GBR and included in the analyses: time of death for ENDs (died within the first 24 hours of life, between the first 24 and 72 hours of life, or between the first 73 and 168 hours of life) and for stillbirths (antepartum, i.e., fetus died before onset of labour, and intrapartum, i.e., fetus died in utero after onset of labour but before delivery); GA at delivery (22-27, 28-31, 32-36, ≥37 completed weeks); and primary and secondary causes of death. Causes of death for ENDs were separated into five groups based on the Wigglesworth classification: preterm birth complications, congenital malformation, birth asphyxia, infection, and other (21, 72). The main criteria used to classify the cause of death has been described previously (21) and include the presence or absence of lethal congenital malformations, birthweight, GA, Apgar score, birth asphyxia, and infection. The information on these variables was trustworthy in the GBR, thus we were able to use this classification with confidence.

Paper II

The main outcome in Paper II was PM. Data on PM cases were extracted from the GBR and the VRS. Indeed, the GBR only registers newborn outcomes before discharge or transfer to another facility. Therefore, the outcomes of newborn who were discharged/transferred during early neonatal period were identified in the VRS. The VRS was also used to validate all livebirths and PM cases identified in the GBR. The agreement between the GBR and the VRS was 99.8%, with the 0.2% difference attributed to home deliveries and deliveries outside of the country.

The main exposure was ANC attendance, data on which were also taken from the GBR. Attended pregnancies were defined as a woman who had at least one ANC visit during any stage of her pregnancy. Women who did not have any ANC visits were considered to have unattended pregnancies. The Social Service Agency collects information on the number of ANC visits for financial purposes, but as it only includes programme-financed ANC visits and not private ones, thus we could not validate GBR information on ANC attendance.

The following variables were extracted from the GBR and included in logistic regression analyses: maternal age (≤19, 20-24, 25-29, 30-34, 35-39, ≥40 years), parity (primiparous, multiparous), education (primary, secondary, higher), and region of residence and delivery (living and delivered in Tbilisi (capital), living in Tbilisi and delivered outside Tbilisi, living outside Tbilisi and delivered in Tbilisi, and living and delivered outside Tbilisi).

Paper III

The two outcomes in Paper III were NICU admission and PM, and data on these outcomes were taken from the GBR. NICU admissions were then validated using a hospitalisation registry, which ensures registration of all patients admitted to hospital, but has no specific information on NICU admissions. Newborn transferred to the NICU who died during the early neonatal period were categorised as PM. Information on NICU admission was unknown for 15 072 (10%) newborn in the GBR. Of these, 41 were found in the hospitalisation registry: 35 were admitted for intensive care due to their condition, urgent situation, and the level of the hospital (only tertiary hospitals have a NICU in Georgia). Thus, we classified those 35 cases as NICU admissions and the remaining cases as NICU non-admissions.

ANC utilisation, measured using the adequacy of prenatal care utilisation (APNCU) index, was the main exposure in Paper III (73). The APNCU index is particularly useful in studying the effect of ANC utilisation on birth outcomes.The index was used to categorise women into four groups by ANC utilisation: those receiving intensive, adequate, intermediate, and inadequate care. Women were assigned to these groups based on the expected number of ANC visits, which was obtained from Georgian guidelines on ANC utilisation, and the observed number of visits, which was collected from the GBR, in order to take into account length of pregnancy. Women who initiated ANC before a GA of 14 completed weeks and attended ≥110% of expected ANC visits were assigned to the intensive care group. Women who initiated ANC before a GA of 14 completed weeks and attended 80% to 109% of expected ANC of visits were placed in the adequate care group. Women who initiated ANC before a GA of 14 completed weeks and attended 50% to 79% of expected ANC visits were assigned to the intermediate care group. And women who initiated ANC after a GA of 14 completed weeks, or attended less than 50% of expected ANC visits were placed in the inadequate care group, as were women without any ANC visit during pregnancy. To assess the importance of timely ANC initiation, before a GA of 12 completed weeks, women were categorised into three groups: ANC initiation up to a GA of 12 completed weeks (reference category), ANC initiation after a GA of 12 completed weeks and before 28 weeks, and ANC initiation in or after a GA of 28 completed weeks.

Similar to Paper II, the variables included in logistic regression analyses were maternal age (≤19, 20-29, 30-39, ≥40 years), parity (primiparous, multiparous), education (primary, secondary, higher), and region of residence and delivery (living and delivered in Tbilisi (capital), living in Tbilisi and delivered outside Tbilisi, living outside Tbilisi and delivered in Tbilisi, and living and delivered outside Tbilisi).

3.3 Statistical analysis

Data were analysed using Stata (StataCorp, College Station, TX, USA) version 15.0, and descriptive statistics for all three articles were displayed as means for continuous variables and percentages for categorical and dichotomous variables. **Paper I** was descriptive study, thus, only descriptive statistics were used.

Paper II - logistic regression analysis was used to estimate the association between PM and unattended pregnancies. The analyses were adjusted for maternal age, parity, education, and region of residence and delivery- confounders identified from a directed acyclic graph (DAG, please see below for more information). Additionally, we calculated the population attributable fraction to estimate the burden of PM cases attributable to unattended pregnancy.

Paper III - logistic regression analysis was used to assess the associations between APNCU index categories and NICU admission or PM. The analyses were adjusted for maternal age, parity, education, and region of residence and delivery. Sensitivity analyses were also conducted by running the same models stratified by the old (four ANC visits)/new (eight ANC visits) ANC programme and term/preterm newborn. The Chi-square test was used to test whether there was a difference in PM/NICU admission proportions before and after implementation of the new ANC programme. We calculated the odds of NICU admission and PM and for late ANC initiation (i.e., after a GA of 12 completed weeks).

3.3.1 Directed acyclic graph

Confounders are defined as pre-existing covariates that are associated with the exposure and the outcome and thus affect the relationship between them. Controlling for all potential confounders minimises the risk of bias (74). There are different approaches to selecting the confounders for any exposure-outcome association. One approach for fitting the 'best' available model is to draw the relationships between variables using causal diagrams (75-77), which was used for model building in **paper II and III**.

The theory of causal diagrams based on directed acyclic graphs (DAGs) centres on a set of assumptions. Using arrows to display the causal association between the exposure, the outcome, and all other known covariates gives researchers the opportunity to identify the minimum set of variables for which one must adjust to detect the real association between the exposure and the outcome. Expert knowledge and existing literature form a large part of the basis of any DAG, but incorrect assumptions are always a possibility, and the presence of incorrect assumptions would render the DAG invalid. We decided to focus on the DAG as a visible method in modern epidemiology. The understanding of all potential relationships in the frame of one particular DAG can be treated differently; in any case, it creates a good basis for discussions on assumptions, potential bias, and further improvements.

3.4 Ethical approval

The PhD project and study protocol were reviewed and approved by the NCDC Institutional Review Board. Additionally, the use of GBR data for research purposes was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2017/404/REK Nord). Further, as stated in the memorandum between the Project CPEA-2015/1-54 "Georgian-Norwegian Collaboration in Public Health" and LEPL "L.Sakvarelidze National Center for Disease Control & Public Health", the secondary, anonymised database of the GBR should be made available only for research, analytic, and scientific purposes.

4 Results

4.1 Overview of data in the Georgian Birth Registry from 2017 to 2019

After excluding all potential outliers, 150 533 women and 152 733 newborn were registered in the GBR from 2017 to 2019. This included 1890 PM cases: 1396 stillbirths and 494 ENDs. This translates into a mean PM rate of 12.3 per 1000 births (95% confidence interval (CI) 11.8-12.9), a mean stillbirth rate of 9.1 per 1000 births (95% CI 8.7-9.6), and a mean END rate 3.3 per 1000 livebirths (95% CI 3.0-3.6) (Figure 6). The characteristics of the study population, from which the study samples in Papers I-III are derived, are provided in Table 1. The birth rate decreased between 2017 and 2019 (from 14.3 to 13.0 per 1 000 population), but the PM rate fluctuated. The stillbirth to END ratio was 2.1 in 2017 and 3.5 in 2019.

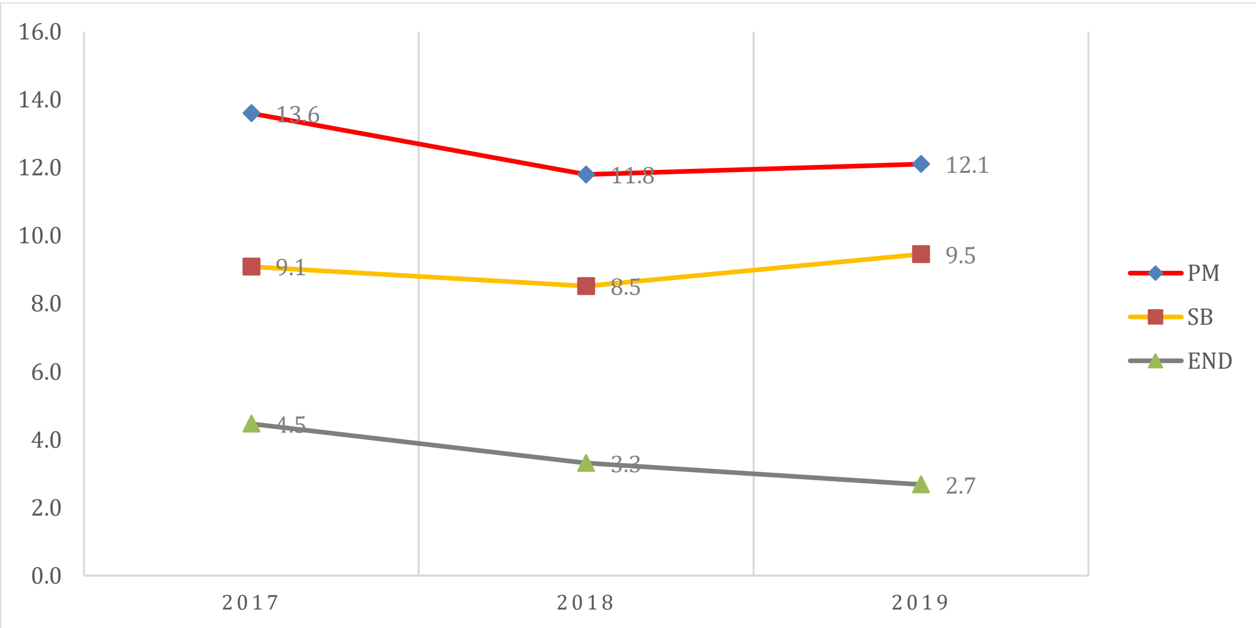

Figure 6. Perinatal mortality (PM), stillbirth (SB) and early neonatal death (END) rates in Georgia, 2017-2019.

Table 1. Characteristics of mothers and newborn registered in the Georgian Birth Registry presented as a column percentage, 2017-2019.

	PM	non-PM
Number of mothers	1802	148 731
Number of newborn	1890	150 843
Maternal age (mean)	30.5 (6.8)	28.8 (5.8)
Maternal age (%)		
>20	2.7	2.5
20-29	46.8	58.5
30-39	41.2	35.4
40-49	9.3	3.6
>49	0	<0.1
Parity (%)		
Nulliparous	39.7	38.7
Multiparous	60.3	61.3
Education (%)		
Primary	10.8	8.2
Secondary	47.7	44.9
Higher	28.6	36
Unknown	12.9	10.9
Marital status (%)		
Single	11.3	12
Married	38	47.8
Unknown	50.6	40.2
Nationality (%)		
Georgian	65.7	68.9
Azerbaijani	8.9	7.3
Armenian	2.8	2.9
Other	1.4	1.6
Unknown	21.2	19.3
Region of residence (%)		
Adjara	11	11.6
Abkhazia	1	0.8
Guria	2.7	2.1
Imereti	11.2	12.1
Kakheti	7.6	7.6
Kvemo Kartli	15.6	12.2
Mtskheta-Mtianeti	1.8	1.9
Racha-Lechkhumi and Qvemo Svaneti	0.4	0.5
Samegrelo and Zemo Svaneti	7	6.9
Samtskhe-Javakheti	3.7	3.8
Shida Kartli	6.7	6.3
Tbilisi	31.3	34.2
Delivery type (%)		
Vaginal	60	55

Vaginal with intervention	6.8	2.7
Caesarean section	33.2	42.3
Multiple birth (%)		
Singleton	90.8	97.2
Twins	8.7	2.7
Triplets	0.5	0.1
Gestational age weeks, mean (SD)	30.5 (5.9)	38.6 (1.8)
Gestational age groups (weeks) (%)		
22-28	44.1	0.4
29-32	16.8	1.1
33-36	16.5	6.4
37-41	22.2	91.8
>41	0.4	0.3
Birthweight g, (mean)	1565 (1087)	3268 (537)
Birthweight groups, g (%)		
<1500	58.3	0.9
1500-2499	17.7	5.4
2500-3499	17.7	58.4
3500-4499	5.3	34.3
≥4500	1	1
Antenatal care visits (mean)	3.6 (2.4)	5.5 (2.6)
Antenatal care visit groups (%)		
0	13.9	5.2
1-3	35.6	13.1
4-6	38	45.1
7-8	9.9	25.9
>8	2.6	10.7
Year of delivery (%)		
2017	38.1	34.9
2018	31	33.6
2019	30.9	31.5

SD: standard deviation, PM: perinatal mortality

Mean maternal age was higher among mothers who experienced PM (PM group) compared to those who did not (non-PM group). The proportion of women with primary education and non-Georgian nationality was also higher in the PM group. A high proportion of women from the regions of Kvemo Kartli and Shida Kartli were in the PM group, and a lower proportion of women in the PM group was from Tbilisi. The overall caesarean section rate was 42.1%, and this rate was lower in PM group (33.2%). Among PM cases, 9.2% were multiple births, while the corresponding proportion in non-PM cases was 2.9%. The mean GA and mean birthweight was lower in the PM group, as was the mean number of ANC visits, which was 3.6 compared to 5.5 in the non-PM group. The disparities between the number of ANC visits was obvious in the PM and non-PM groups: 13.9% of women in the PM group did not have any ANC visit during pregnancy, while this was the case for only 5.2% of women in the non-PM group. Additionally, the proportion of women who received between 1 and 3 ANC visits was higher and the proportion of women who received more than 6 ANC visits was much lower in the PM group.

4.2 Paper I

In Paper I, we aimed to determine the incidence and the causes of stillbirths and ENDs in Georgia in 2017. The PM rate in Paper I was 13.6 (95% CI 12.6-14.5) per 1000 births; stillbirth and END rates were 9.1 (95% CI 8.3-9.9) per 1000 births and 4.5 (95% CI 3.9-5.1) per 1000 livebirths, respectively. Eighty-five percent of stillbirths were antepartum and 9% were intrapartum; time of death for the remaining 6% was unknown. The majority of ENDs (40%) died between the first 73 and 168 hours of life, 30% died within the first day of life, and 30% died between the first 24 and 72 hours of life. Twenty-three percent of stillbirths and 17% of ENDs were born at a GA of ≥37 weeks. In addition, 28% of stillbirths and 58% of ENDs were delivered by caesarean section. The stillbirth to END ratio was 2.1.

Eighty percent of stillbirths had an unknown cause of death, while no ENDs had a missing or unknown cause of death. Causes of stillbirths included maternal conditions (7.8%) and placenta and umbilical cord complication (5.2%). The most common cause of END was preterm birth complications (58%), followed by congenital malformations (23%), and birth asphyxia and infections (7% each). The remaining 5% had ‘other’ as the cause of death. The causes of END differed by GA at delivery: the most common cause of death among extremely preterm ENDs (delivered at a GA of 22-27 weeks) was preterm birth complications (89%); this was also the case for very preterm ENDs (delivered at a GA of 28-31 weeks, 72%). The leading cause of death for moderate preterm ENDs (delivered at a GA of 32-36 weeks) was congenital malformations (45%). Similarly, congenital malformations were the cause of death in 39% of ENDs delivered at a GA of >37 completed weeks, followed by other causes (25%) and infection (19%).

4.3 Paper II

In Paper II, we aimed to assess the association between unattended pregnancies and PM from 2017 to 2018. The proportion of unattended pregnancies was 5.6% (n=5706). The PM rate among unattended pregnancies was 28.7 (95% CI 25.9-34.7) per 1000 births, almost three times higher than the rate observed among attended pregnancies (10.7, 95% CI 10.0-11.3 per 1000 births). After adjustments for potential confounders, women with unattended pregnancies had more than two times higher odds of experiencing PM, compared to women with attended pregnancies (adjusted odds ratio (AOR) 2.21, 95% CI 1.81-2.70). Maternal age of 45 years or more was associated with 3.5 times increased odds of experiencing PM, compared to women aged between 25 and 29 years. Primiparous women had 43% increased odds of PM compared to multiparous women. Primary education was also associated with 33% increased odds of PM when compared to secondary education, while higher education was inversely associated with experiencing PM. Given a causal relationship, if women with unattended pregnancies had attended at least one ANC visit, 5.9% of PM cases could have been avoided, which translates into 71 singleton PM cases between 2017 and 2018.

4.4 Paper III

Paper III was conducted in order to evaluate the associations between ANC utilisation and NICU admission and PM in Georgia between 2017 and 2019. The proportion of unattended pregnancies was 5.3% (7897 singleton mothers). The distribution of APNCU index categories showed that 16% of women received inadequate care, 10% received intermediate care, 38% received adequate care, and 36% received intensive care.

Women in the intermediate care group had the lowest PM rate (6.9 per 1000 births), END rate (2.1 per 1000 livebirths), and stillbirth rate (4.8 per 1000 births), and they had the lowest proportion of NICU admissions (7.0%) and preterm births (4.8%). The PM (16.9 per 1000 births), END (3.9 per 1000 livebirths), and stillbirth rates (13.1 per 1000 births) were highest in the inadequate care group, as was the proportion of NICU admissions (8.8%) and preterm births (8.7%). Women in the inadequate care group had 18% (AOR 1.18, 95% CI 1.02-1.36) increased odds of experiencing PM and 16% (AOR 1.16, 95% CI 1.09-1.23) increased odds of delivering a newborn who was admitted to the NICU, when compared women in the adequate care group, and after adjusting for maternal age, parity, education, and region of residence and delivery. The PM rate during the old ANC programme, was 11.1 (95% CI 10.4-11.8) per 1000 births, compared to 12.2 (95% CI 11.4-13.1) per 1000 births in the new ANC programme, and the difference between these rates was statistically significant (p=0.04). The proportion of NICU admissions in the old and new ANC programmes was 6.8% (95% CI 6.6-7.0) and 9.1% (95% CI 8.8-9.3), respectively (p<0.01).

Newborn of women in the intensive care group had 16% increased odds of NICU admission (AOR 1.16, 95% CI 1.11-1.22) compared to those whose mothers were in the adequate care group. The results for experiencing PM in the intensive care group were not statistically significant (AOR 0.91, 95% CI 0.81-1.03). The odds of experiencing PM in the intermediate care group were 43% lower (AOR 0.56, 95% CI 0.45-0.70) than in the adequate care group. The results for NICU admission observed in the intermediate care group were not statistically significant (AOR 0.97, 95% CI 0.90-1.05).

The association between ANC initiation and NICU admission or PM was not statistically significant, except for ANC initiation after a GA of 12 completed weeks and before 28 weeks, which increased the odds of NICU admission by 14% (AOR 1.14, 95% CI 1.06-1.24) compared to those who initiated ANC before a GA of 12 weeks.

5 Discussion

5.1 Main findings

The overall aim of the PhD project was to identify the causes of PM as well as the impact of modifiable factors, like ANC utilisation, on PM in Georgia. The discussion is based on the three above-mentioned papers. Initially, the included papers confirm that the PM rate in Georgia is higher than that in all other European countries (78). When compared with neighbouring countries, only Armenia has a higher PM rate than Georgia (78). There was no evidence of a decline in the stillbirth rate from 2017 to 2019; only the END rate decreased slightly. Although Figure 4 demonstrates a decrease in the stillbirth rate from 2017 to 2018, followed by a slight increase in 2019, the END rate at that time was steadily decreasing. Even though a new ANC programme that adheres to WHO recommendations was implemented in 2018, the proportion of stillbirths has increased over the last 3 years. Based on the Wigglesworth classification, the main causes of END were preterm birth complications and congenital malformations, displaying a picture similar to that observed in high-income countries.

We identified a possible misclassification between stillbirths and ENDs in Paper I, which complicated the subsequent analysis of the factors affecting PM. This demonstrates the necessity of proper reporting of time of death for fetuses and newborn. The misclassification findings are discussed below.

Another important finding was that ANC attendance was strongly associated with the PM rate in Georgia. The odds of PM were significantly higher (more than double) for unattended pregnancies and for those in the inadequate care group when compared to attended pregnancies and those in the adequate care group. Targeting women who are more likely not to attend ANC may reduce PM cases, specifically those related to avoidable and preventable causes.

5.2 Possible misclassification of stillbirths and early neonatal deaths

Our study revealed the importance and possible difficulties of proper classification of PM cases in Georgia. Distinguishing stillbirths from ENDs, especially ENDs that died during the first hours of life, seemed to be the main barrier in analysing the subsequent causes of stillbirths and ENDs in Georgia. Contrary to expectations, 70% of ENDs occurred after the first 24 hours of life. This finding runs counter to global estimates, which suggest that 50% to 65% of ENDs occur during first 24 hours of life. Indeed, as a general rule, the proportion of ENDs should decrease as time since birth increases (5, 6). A study of neonatal mortality in 186 countries showed that more than 50% of ENDs occur during first 24 hours of life (6). This proportion was even higher in upper-middle-income countries when compared to low-income countries with limited resources. The reason for this may be the increased possibility for newborn survival in countries with advanced medical technologies and human resources. Unavoidable newborn deaths usually occur during the first several hours of life, and avoiding preventable deaths is more likely in high-income countries.

WHO global, regional, and country estimates of neonatal morality and PM suggest a mean stillbirth to END ratio range of 0.6 to 1.7 for WHO subregions and of 1.2 for Georgia (8). In our study, this ratio was 2.1 in 2017 and 3.5 in 2019. Moreover, although a ratio below 1 indicates underreporting of stillbirths, high values may demonstrate misclassification, or overreporting of ENDs. Moldova stands as an outlier, with a ratio of 3.2. The most likely explanation for the high ratio in Moldova is thought to be misclassification (79).

Another important finding was that only 9% of stillbirths were intrapartum, and 85% were antepartum. Other studies have shown that more than 33% of all stillbirths are in fact intrapartum (8, 80, 81). The distribution of antepartum and intrapartum stillbirth proportions varies by country (82) and depends mainly on access to healthcare and the quality of ANC and obstetric practice. In general, the presence of more intrapartum stillbirths than antepartum stillbirths is a recognition of high-quality ANC and obstetric practice (79).

In order to assess causes of death, we classified them separately for stillbirths and ENDs. Eighty percent of stillbirths causes of death were registered as “unexplained”, which is a higher proportion than has been reported elsewhere (between 32% and 41%) (18-20). Based on the Wigglesworth classification, the most common cause of ENDs was preterm delivery complications (58%), followed by congenital malformations (23%) (appendix 1). The proportion of ENDs due to congenital malformations varies by country: the proportion is higher in high-income countries (>40%) (5) and lower in low-income countries (3%) (83). The proportion of ENDs due to asphyxia was 7% in our study, while in low- and middle-income countries this proportion is 25% (5). The higher proportion of unexplained stillbirths and that of ENDs due to congenital malformations may suggest a misclassification of asphyxiated newborn as unexplained stillbirths, which would artificially increase the proportion of congenital malformations in the causes of ENDs.

The idea of misclassification of stillbirths and ENDs has been previously used as an explanation for high proportions of stillbirths in combination with causes of death (13, 84, 85). In our study, i) a higher proportion of antepartum and unexplained stillbirth; ii) a lower proportion of asphyxiated newborn; and iii) an overabundance of ENDs occurring after 24 hours of life, lead us to believe that there is substantial misclassification between stillbirths and ENDs in Georgia. Concordantly, the similarity of causes of death in Georgia to high-income countries further increases the suspicion of misclassification. The proportion of congenital malformations is too high when compared with the proportion of asphyxia. Most likely, asphyxiated newborn who died during the first hours of life were consistently misclassified as stillbirths. This would explain some disparities in rates and proportions. Specifically, our study revealed a likely underestimation of intrapartum-related ENDs misclassified as antepartum stillbirths. For this reason alone, in any country where such misclassification occurs, the possibility to study the contributing factors of stillbirths and ENDs separately is limited. The obvious question that remains is whether this misclassification occurred only in the GBR, or if it is also present in corresponding medical files. To find out, we have initiated a validation study to compare the contents of 1250 random medical files, in addition to PM cases (n=208) for 2019, with data from the GBR. The results from this study are pending, but if the medical files coincide well with the GBR, Georgia has a misclassification - problem that needs immediate attention.

The time of death for ENDs is strongly associated with the cause of death, and this was also observed in our results. Intrapartum-related deaths, i.e., intrapartum stillbirth and END shortly after birth, are largely avoided by interventions during delivery. Thus, intrapartum-related death is determined mostly by the quality of obstetric services. On the contrary, antepartum stillbirths are mostly recognised as a reflection of gaps in ANC and are attributed to a lack of ANC. The PM rate is high in Georgia, and we set out to identify how many of these deaths can be linked to unattended pregnancies.

5.3 Unattended pregnancies

One important finding was that the odds of PM in unattended pregnancies were twice as high as those observed in attended pregnancies. This finding can be further extrapolated to: women without any ANC visits had twice the risk (AOR 2.21, 95% CI 1.81-2.70) of experiencing PM compared to women who attended at least one ANC visit. These results corroborate findings from several other studies (86-89). Further, we assumed that not attending any ANC visit would have a causal effect on PM, thus we calculated the population attributable fraction in order to estimate the proportion of PM cases that could be avoided if ANC were provided. For 2-year study period, this fraction was 5.9% which means that 5.9% (n=71 cases) of singleton PM cases could potentially have been prevented if all women had attended at least one ANC visit during pregnancy.

The positive association between routine ANC and favourable birth outcomes is well established (44, 89-91). There is a growing body of evidence that suggests the substantial positive impact that surveillance, risk management, and proper planning during pregnancy have on the health of mothers and their newborn (86, 92-94). For comparison, with the exception of Latvia, the proportion of unattended pregnancies in the whole Euro-Peristat project was less than 0.2%. Our results indicate that Georgia has a higher proportion (5.6%) of unattended pregnancies than other European countries. Younger (≤19 years) and older (≥40 years) multiparous mothers with lower education were less likely to attend ANC, as were mothers who resided outside but delivered in Tbilisi. Educational campaigns with a focus on reproductive health, involving healthcare providers and local health communities in promoting

ANC initiation, and improved financial support would increase ANC coverage. Initially, older multiparous mothers with lower education should be defined as the target group.

These results provide further support for the generally accepted hypothesis that attending ANC improves birth outcomes. Even one ANC visit has an effect on reducing PM rates. Measuring ANC utilisation is critically important for addressing questions about properly conducted ANC. Therefore, as a final step, we assessed the relationship between timing of ANC initiation, number of observed ANC visits, and the most severe perinatal outcomes: NICU admission and PM.

5.4 Antenatal care utilisation

Not only not attending antenatal care, but also the number of attended ANC visits was significantly associated with NICU admission and PM. Newborn survival is steadily increasing worldwide because of improved technologies, medication, and evidence-based interventions. Newborn admitted to NICU are considered the most severe cases. Therefore, decreasing PM rates may come in tandem with increasing NICU admissions, as more newborn have the chance of survival if admitted to intensive care. Therefore, in our analysis, NICU admission was defined as a secondary outcome. In line with other studies (95, 96), our results suggested that women in the APNCU index categories of inadequate or intensive care had a higher rate of NICU admission when compared to women who received adequate care. One explanation for this finding might be that some proportion of sicker mothers received intensive care, and insufficient care increases the chance of the poorer outcomes. However, the PM rate was only higher among women who received inadequate care, when compared to women in the adequate care group.

The results and interpretations for these two outcomes differed in our study. Newborn of mothers in the intensive care group had higher odds (16%) of NICU admission compared to the adequate care group. Generally, women in the intensive care group have higher odds of adverse pregnancy outcomes, because complications during pregnancy are mediated by intensive ANC, thus the odds of PM, low birthweight, and preterm birth in the intensive care group increase (32, 94, 97). However, the intensive care group (36%) also contained a significant proportion of healthy pregnancies among women who prefer/pay for extra visits (98, 99). The two groups are indistinguishable in terms of PM in our data, hence the deliveries in the intensive care group were biased towards appearing healthier than the frequency of visits might indicate. The suspicions of bias are further strengthened by the fact that the intensive care group had no increased odds of PM.

Women who received intermediate care had the lowest odds of experiencing PM, which suggests that this group was mostly represented by low-risk pregnancies. The odds of NICU admission in this group seemed to be similar to that of the adequate care group, with borderline significance. The inadequate care group carried the highest odds of both outcomes: women who received inadequate care had 16% increased odds of NICU admission and 18% increased odds of PM.

There is growing evidence that inadequate care or lack of ANC is a determinant of poorer newborn outcomes, such as NICU admission and PM (24, 32, 34, 39, 44, 81, 95, 100-104). In their systematic review, Bhutta *et al* suggested that a moderate level of evidence support that the promotion of appropriate care seeking and ANC had an impact on maternal and newborn mortality (92). The level of evidence was based on the Grading of Recommendations Assessment, Development and Evaluation assessment (105). Additionally, a study from the United States showed that decreased care during pregnancy linearly increased the risk of preterm birth, stillbirth, END, late neonatal death, and infant death (39). Maternal education, age, socioeconomic status, reproductive health, and ethnicity are recognised as determinants of seeking ANC (18, 39). Another study showed that more women in low- and middle-income countries are following global recommendations, and that patterns of care are improving. The quality of ANC differs across countries by income level. Implementation of new ANC programmes with an increased number of visits can improve the proportion of attended pregnancies; however, quality control is essential. Besides measuring overall ANC utilisation, we analysed the difference between the old and new ANC programme by NICU admission and PM.

5.4.1 Implementation of new antenatal care recommendations

The old ANC programme consisted of four financed ANC visits for every pregnant woman if care was initiated before a GA of 12 weeks. The new ANC programme, which was implemented on 1 February 2018, provides eight financed visits for every pregnant woman if care is initiated before a GA of 12 weeks. Contrary to expectations, no significant improvement was found in NICU admissions or PM rates after implementation of the new ANC programme (Paper III). A larger sample size and longer study period would, of course, be preferable, but these findings may suggest that simply increasing visits for all women is less effective than individually tailored care and subsequent planning of ANC. Revising the quality of care provided is essential. In low- and middle-income countries, even if ANC utilisation is adequate, most preventable deaths are not avoided (106, 107).

Finally, our study revealed that NICU admissions actually increased after the implementation of the new ANC programme. This may be a result of improved risk assessment for newborn and proper NICU admission, i.e., when it is actually necessary. Assessment of the effectiveness of the ANC programme should be monitored for several years in order to plan further interventions and identify the cost-effectiveness of the programme.

5.4.2 Timing of antenatal care

In Georgia, 86.8% of pregnant women attended their first visit while in their first trimester. Most likely this high proportion is a result of the fact that visits are only financed by the government if ANC is initiated before a GA of 12 completed weeks. Women who seek care later in pregnancy must pay for ANC visits out of pocket, which can be a barrier for women who decide to attend ANC after the first trimester and the high rate of unattended pregnancies may be influenced by this restriction. Removing this 12-week deadline could potentially improve the coverage of ANC attendance?

Further, we revealed that timing of ANC, independent of the number of ANC visits, does not have a significant impact on NICU admission or PM. Our finding is supported by previous research, which suggests that ANC initiation late in pregnancy does not have a significant negative impact on birth outcomes, after adjusting for potential confounders (108, 109). It is generally accepted that around 50% to 70% of embryos die before the pregnancy is even recognised. Thus, pregnancies that survive past a GA of 12 weeks have already passed the most critical period (110). Inequality between countries in care initiation and amount of ANC received is, are two main determinants of poorer health outcomes (107).

Women in low- and middle-income countries are more likely to initiate ANC later than those in high-income countries (109). Early (before a GA of 12 weeks) ANC visit coverage increased worldwide from 40.9% in 1990 to 58.6% in 2013, which represents the latest available data, and estimates of coverage for high- and low-income regions were 84.8% and 48.1%, respectively (37). This demonstrates large global and regional discrepancies. The Euro-Peristat project is using early ANC visit as one indicator of perinatal health. In 2010, only a few countries had an early ANC initiation coverage below 90% (Ireland, Lithuania, Malta, the Netherlands, and Romania).

Despite increasing rates of ANC attendance in recent decades, the inconsistency of provided care during pregnancy is obvious. Encouraging women to initiate ANC earlier in pregnancy may help them receive adequate care; further, financial support for late attenders may decrease the rate of unattended pregnancy, however, we cannot suggest that early ANC initiation alone decreases the risk of NICU admission or PM.

5.5 Maternal characteristics

In Paper II, we presented the associations between maternal characteristics and PM in Georgia. Discussion points not fully elaborated in the articles are included below.

5.5.1 Maternal age

Our study showed that advanced maternal age is linked with increased odds of PM. Based on our study sample, mothers aged over 40 years had 3.5 times increased odds of PM when compared to mothers aged 25 to 29 years. However, results on younger mothers were not statistically significant, thus mothers below 20 years of age did not have increased odds of PM. Unless there was a history of PM, younger age was not associated with PM in a previous study (111). A positive association between older mothers and the risk of adverse birth outcomes has been suggested in previous research (112, 113). The average age of mothers at first childbirth was 27.1 years in our study sample, which is lower than in other European countries, where the average age at first childbirth is 29.3 (114).

5.5.2 Parity and education

Primiparous women had 43% increased odds of PM, compared to multiparous women, which is in line with other studies (115). Higher education was negatively associated with adverse birth outcomes: women with higher education had 44% decreased odds of PM compared to those with secondary education, while primary education carried 33% increased odds of PM. The association between maternal education and birth outcomes has been demonstrated before, and our results match those observed in earlier studies (116, 117).

Studying maternal knowledge of pregnancy- and delivery-related topics is essential. Indeed, the reasons women are not attending ANC visits may be linked to their obstetric history and to their knowledge on the situation at hand. Younger or older age, low education level, being single, being an ethnic minority, as well as unplanned pregnancies, high parity, and obstetric history are all major individual determinants of not seeking ANC (118). In Georgia, people tend to receive higher education; however the proportion of the population employed in their field of study is not that high. Women who get married at an earlier age are more likely to quit university or school, compared to women who are not married. Ethnic minorities are more likely not to receive an education and to get married at an earlier age than Georgians. We identified an association between lower education and PM; however, this association was not significant in women younger than 19 years of age. Further, education on the topic of reproductive health is not optimal. Women who did not complete their secondary education or who quit university may be a good target group for improving women's education on these subjects.

5.5.3 Region of residence and delivery

Our results further revealed significant differences between PM rates and NICU admission by region of residence and delivery. If women resided outside Tbilisi and gave birth in Tbilisi, their odds of experiencing PM were two-fold to those women who both resided and delivered in Tbilisi. Women who resided and delivered outside of Tbilisi had the lowest odds of PM. These findings have an explanation: women who reside outside Tbilisi and deliver in Tbilisi often represent complicated cases that are transferred to specialty clinics in Tbilisi, whereas women who both resided and delivered outside Tbilisi likely represent uncomplicated, low-risk pregnancies. Further, the proportion of mothers who attended at least one ANC visit during pregnancy varied by region of residence, which can be explained by the geographical distribution of ANC centres and medical facilities in the country. Additionally, it has been reported that women living in rural areas are less likely to attend ANC than women living in urban areas (119). Accessibility to healthcare in Georgia has improved; however, it might be pertinent to question the equality of delivery of medical services between rural and urban areas in the country. Implementing region-specific objectives for improving quality of care and better remuneration for healthcare providers might be good first steps in solving the inequalities between rural and urban areas.

5.6 Gestational age

In Paper II, we showed a clear decrease in PM with increasing GA at delivery. The preterm birth rate was 8.7%, and 77% of PM cases were delivered before a GA of 37 weeks. In Europe and other high-income settings, the preterm birth rate is between 5% and 9%, and 75% of PM cases are preterm (120). This indicates that preterm birth is not particular unique contributor to the inflated PM rate in Georgia. GA-specific PM varies widely and is significantly influenced by patterns of GA at delivery, as well as by registration differences between countries (121). Preterm, SGA, and low-birthweight newborn all have a higher risk of mortality, severe morbidity, and long-term adverse health outcomes (79, 122-124). GA at delivery is the single most significant determinant of birth outcome because as GA decreases, mortality increases up to 100%.

Our results also demonstrated a trend consistent with that reported in other studies: PM rates among unattended pregnancies were higher for each GA compared to attended pregnancies, but the differences between the rates were larger after a GA of 36 weeks. The management of preventable conditions during ANC visits have larger effects later in pregnancy, and previous research showed an increased impact of ANC on neonatal deaths and stillbirths in the third trimester (36, 125). However, when addressing the association between ANC utilisation and PM in Paper III, we were unable to adjust the analyses for GA or identify the specific effect of ANC at each GA due to a lack of information on maternal morbidity, which is a major contributor to preterm birth. We believe that preterm birth should not be treated as a single contributor to PM; instead comprehensive analyses of maternal conditions during pregnancy should be carried out.

Further, we analysed the association between ANC utilisation and NICU admission and PM by preterm birth. Not surprisingly, inadequate care carries higher odds of NICU admission or PM for women who reached a GA of 37 weeks and delivered at term. A comparison of the findings with those of other studies confirms that the impact of adequate ANC increases with increasing GA (36, 90).

6 Methodological considerations

6.1 Inconsistent definitions

We used definitions of stillbirth and ENDs which are recognised by the MoH of Georgia and are in line with most countries' guidelines. However, lack of consistent definitions and terminology makes global comparison of PM rates difficult, especially between low- and high-income countries (126, 127).

In addition to a decrease in PM rates, many countries have achieved significant improvements in reporting newborn deaths in their routine systems and vital statistics. Better registration generally leads to an increase in mortality rates, thus the reduction we witnessed might be larger than the numbers show. However, there are still challenges with data provision. Firstly, a single internationally accepted definition of stillbirth does not exist. Even in high-income countries, different approaches are used to register stillbirths and infant mortality (126, 128). Using birthweight and GA as thresholds gives inequivalent results, due to the occurrence of fetal growth restriction, SGA, and large for gestational age newborn (128). Secondly, not every country routinely collects information on stillbirths. In some settings, weighing a stillborn is not culturally accepted, and in several countries, for example Russia, livebirths are only registered after surviving a certain period beyond birth (129). Thirdly, assessing the real GA at delivery for stillbirths or ENDs is a problem, and despite improvements in data sources and systems, they are still not complete (130). All these factors complicate global comparisons of mortality rates because of the underreporting of deaths in countries with weak registration systems compared to high-income countries. This makes it difficult to measure the real burden of PM. The Euro-Peristat project illustrated that, due to the different thresholds for stillbirth, only those who died after a GA of 28 weeks can be compared between European Union countries, as recommended by the WHO, thus highlighting the importance of comparable data on maternal and child health indicators (16). The hope is that all deaths after a GA of 22 weeks will be counted and compared in the future. The main argument for using this threshold is to identify provision of care, caesarean section rates, and birthweight for these early gestations. In most countries, GA is used to determine stillbirth, and if GA is not available, birthweight is used. Defining stillbirth by birthweight (usually under 500 grams) leads to lower stillbirth proportions than when using GA, and the use of birthweight tends to cause underreporting (127). Most high-income countries have a legal definition of stillbirth that is used for reporting; however there is variation in the threshold of GA that determines stillbirth, ranging from a GA of 16 (Norway) to 24 (United Kingdom) weeks, which limits the possibility to make proper comparisons (127). Therefore, both improving data quality and agreeing on uniform definitions are vital for further health improvements. Countries should mandate that all stillbirths occurring at or after a GA of 22 weeks be registered, and they should set a clear border between late termination of pregnancy and stillbirth (121).

In our data, we assumed that some stillbirths and ENDs had been misclassified. This means that it is possible that not everyone in charge precisely registers the time of death of a fetus or newborn, which obviously complicates comparisons and may bias conclusions. The necessity of registering time of death precisely is an issue for other countries as well (127). In accordance with cause of death, reporting time of death properly is crucial if researchers are to analyse the underlying factors and conditions of death. Careful collection of these data is critical to guide the prevention of stillbirths and ENDs.

6.2 Classification of causes of death

Eighty-one new and modified contemporary classification systems for causes of stillbirth and neonatal death exist in the world, including underlying causes of death (40 of which are considered comprehensive) (131). Agreement between these systems is not optimal, and consistency is essential to any classification (132). The choice of classification system is mostly based on the available data on each death and the need for subsequent analysis (133). This was our rationale behind the choice of using the Wigglesworth classification system. All such systems have their own approach for assigning causes of death, which depends on the method of classification. Therefore, the proportion of main causes can differ by the classification used due to diverse interpretations of direct and indirect causes of death.

Stillbirths and ENDs are usually the result of a complicated chain of events, but classifying one single cause of death for each case is essential from an epidemiological point of view (72). The best way to classify causes of death is to use hierarchical models, in which the aetiological, i.e., primary, cause of these events is obvious. However, detailed and comprehensive data are required. The Wigglesworth classification with the NICE modification, which was used in our study, is simple to apply, does not require pathological findings, and the results have clear implications for clinical management (21). However, this approach does not allow one to analyse the chain of events before death. For example, birth asphyxia, which can lead to death in the presence of other contributing factors, cannot be presented in the classification (72). NICE, the causes of death and associated conditions classification, and the classification of stillbirth by relevant condition at death classification provide more groups and were created for the purpose of classifying the biological causes of death. Those classification systems were generated to reduce the predominance of the unexplained or unknown category (72, 134, 135). Due to the fact that an autopsy is not routinely conducted for stillbirths or ENDs in Georgia, there is no pathophysiological understanding of each cause of death. Therefore, we could not use more a comprehensive classification system to address single causes of death for PM, which would have given us a better understanding of the proportion of potentially avoidable deaths. Although this could have been helpful to demonstrate the impact of ANC on PM, it does not underestimate the importance of the presented results.

The lack of reliable cause of death data has been identified in countries with the highest burden of PM (136). The existing data and the source of classification may lead to differences when comparing results across countries. Additionally, even high-quality data can have registration difficulties. For instance, ICD-10 codes are not ideal for registering causes of PM; the upcoming ICD-11 classification may provide a more appropriate coding system for neonatal deaths (137).

All these issues may lead to complications when comparing single causes of death across the world. Even when there is no autopsy, doctors still have to specify a cause of death for newborn in Georgia. When an autopsy is lacking, the cause of death can be misinterpreted even when using comprehensive classification systems. Implementation of systematic autopsies would be helpful in identifying the exact time and direct cause of death.

6.3 Directed acyclic graphs

We used DAGs to select confounders, i.e., common causes of exposures and outcomes, and to identify potential routes of bias between them. Another possibility is a data-driven procedure. However, the main limitation of the latter method is the use of one particular dataset as a baseline for making decisions on confounders. Another approach for fitting the 'best' available model is drawing the relationships between variables, i.e., using causal diagrams. Using one-way direct arrows, an acyclic graph can be drawn, which illustrates measurable variables for unconfounded effect estimates. We assumed that there was a causal relationship between ANC utilisation and PM. We created and interpreted the DAG based on existing literature and background knowledge. Therefore, we are assuming that the observed confounders and colliders are appropriately selected and were measured without measurement errors.

One major discussion in perinatal epidemiology centres on whether or not to adjust for GA when studying the association between pregnancy-related exposures and newborn outcomes. In some scenarios, GA at delivery is on the causal pathway between exposures, maternal and newborn conditions, and mortality; thus, sometimes GA plays the role of a mediator. Therefore, from a scientific point of view, GA might be mislabelled as a confounder when it is actually an intermediate factor (138), and adjusting for it may introduce bias, which could result in under- or overestimated conclusions (139). Due to the fact that mortality and GA at delivery are interlinked conditions, potential confounders for addressing the research question should be selected with caution.

The main limitation of using DAGs is the use of incorrect assumptions, which could inject bias into decisions on selected confounders. Further, DAGs are only as good as the background knowledge used to create them. Finally, DAGs assume that the associations are direct and acyclic, but for some biological, clinical, and epidemiological processes this may not be the case (140). In other existing methods to select confounders, covariates, and colliders have the same limitations.

6.4 Guidelines for antenatal care and antenatal care utilisation

6.4.1 Guidelines for antenatal care

The aim of our research was not to assess the quality of ANC and its relation to PM. Therefore, we did not measure the content of, or services provided during ANC visits, even though one contributor to the association between number and timing of ANC and PM is ANC quality. Despite the fact that one guideline is accepted in Georgia for all healthcare providers, it has not yet been determined if every ANC visit covers the same content across the country. Diversity in the provision of core ANC services is the main barrier to comprehensive comparisons of study results. There are different indicators and tools that can be used to assess the quality of ANC, which complicates comparisons between countries (30, 141). The ANC guidelines from 25 European Union countries showed large variation in the number of recommended tests performed during pregnancy (142). As proposed guidelines and available evidence differ by country, the explanations we give for our study results may not be directly applicable to every study population and cannot be generalised. However, comparing the adequacy of ANC packages quantitatively provides a landscape for analysis and future research.

Comprehensive understanding of the quality of ANC in Georgia is lacking, as is information on women's satisfaction with the care they receive. Thus, we cannot conclude if all ANC centres are following the proposed guidelines, or whether care is adequately conducted, even if the number of visits were optimal, which can be seen as a challenge when interpreting our results.

6.4.2 Measuring antenatal care utilisation quantitatively

The groups of ANC utilisation in our study might have been different if we had used another index. The assessment of ANC is heavily shaped by the method used, and the term 'adequate' is not uniformly defined. Several different indices have been conceptualised to define adequate ANC care. Most of these indices are based on the number of ANC visits and time of ANC initiation. The 1973 Kessner index was a first attempt at such an index, and it was a major achievement in perinatal health research. It stratified ANC into three groups: adequate, inadequate, and intermediate (73, 143). However, due to several limitations of the Kessner index, we considered the later developed APNCU index to be a better tool for assessing ANC. Several different indices have been proposed by different authors, like the Graduated Index of Prenatal care Utilisation, APNCU-1 modification, and APNCU-2 modification (144). One study compared the association between birth outcomes (e.g., SGA, preterm birth, and infant mortality) and ANC using four indices and observed substantial difference (144). Therefore, we may have obtained different results had we used another index. For instance, when using the Graduated Index of Prenatal care Utilisation, women with no ANC visits are placed in a separate group, while in the APNCU index they are included in the inadequate care group. Principal differences between indices may slightly lower the possibility to compare our results to research that used another index.

There is broad variation in perinatal health indicators across European Union countries (145). The content and timing of care in pregnancy (CTP) tool was suggested as a method to address the adequacy of content of care (146). CTP tool is developed to assess how well the ANC reflects national or international guidelines. It was revealed that, despite the extra number of ANC visits in the intensive care group, this care was not always classified as appropriate based on the CTP tool. Moreover, as has been was found in other studies, the number of ANC visits alone was not significantly associated with preterm birth. In contrast, the association between the CTP and preterm birth was obvious (147). This suggests that attending extra visits is not the same as receiving ‘extra’ care; thus, the implementation of the new ANC programme in Georgia should be evaluated with caution. Finally, one source of weakness in this study that could have affected our assessment of the number of ANC visits was that we could not validate ANC utilisation in another data source.

6.5 Missing or incomplete data

Functionalities inserted in the system, like built-in validations and limitations for outliers or inconsistency, improves data quality. Requirements for quality assurance were defined before the GBR was implemented, and they were later integrated into the system. A GBR data audit is pending as a way of quality control. Missing information is a challenge for any newly implemented health registry. However, there were very few missing values (most variables <1%) for the variables used in our analysis and compared to the first analysis of the GBR conducted based on 2016 data (71). Indeed, the amount of missing information on selected variables in the GBR since 2017 was lower than in 2016 (maternal age, GA – 0%, parity – 0.08%). We assumed that the small proportion (<5%) of missing information on potential confounders in our study would not affect our results.

The data on maternal morbidity were not complete, and we could not include maternal complications in the analysis due to substantial amounts of missing information. In 2019, the registry office of the NCDC initiated a validation study for quality assurance and improvement. Preliminary results show that, when compared to medical files, the information on maternal health and complications during pregnancy is underreported in the GBR, while all other selected variables are comparable and show a more than 95% compliance.

The imperfect access to maternal morbidity in our analysis can be seen as a limitation of the study. Adjusting for maternal morbidity prior to and during pregnancy could help us determine the proportion of women who might have a medical background that may have required extra ANC visits. With this information, our discussion of the overutilisation of ANC could be more elaborate.

6.6 Unmeasured confounding

The effect of unmeasured confounders and their potential impact on study results should always be considered in research. There are several variables we were not able to identify, and thus adjust for, in the analysis. For instance, a previous study on the determinants of ANC showed that socially vulnerable women are at higher risk of having fewer ANC visits (148) and PM (149, 150). Measuring and including socioeconomic status in the analysis might have yielded more accurate results in our study. Further, the proportion of unattended pregnancies includes unintended pregnancies, which is strongly associated with both the exposure and the outcome in our study, as well as lower ANC utilisation (151) and child mortality (152). However, data on socioeconomic status and unintended pregnancy were not available.

Maternal morbidity during pregnancy affects newborn health outcomes and has an effect on woman's view of ANC. Due to underreporting of the most common pregnancy complications in the GBR, we were unable to determine whether these women have an elevated risk of PM. Moreover, a woman's health prior to pregnancy and any health preparations made for having a baby are relevant factors for both the mother and the newborn, but these data were not available in our study. Obstetric history, like previous abortions and stillbirths, were not included due to the unreliability of these data in the GBR, and this variable can be considered a confounder in our analysis. Diseases prior to and during pregnancy could help us to distinguish between low- and high-risk pregnancies, and to analyse these groups separately. Therefore, socioeconomic status, unintended pregnancies, maternal diseases before and during pregnancy, and obstetric history can be considered as unmeasured confounding.

7 Conclusion

Asphyxiated newborn may be misclassified as antepartum stillbirths in Georgia. The country has a high proportion of unexplained and antepartum stillbirths. The causes of ENDs, preterm birth complications, and congenital malformations in Georgia are similar to those in high-income countries. The high PM rate in Georgia may be a result of the high proportion of unattended pregnancies. More than 5% of pregnant woman did not attend any ANC visits, and the odds of those women experiencing PM was twice as high. Further, almost two-thirds of the women who delivered between 2017 and 2019 in Georgia did not receive adequate care. Decreasing the proportion of unattended pregnancies may to lead to a decrease in PM. Additionally, increasing the number of ANC visits from four to eight alone did not improve newborn outcomes. Timing of ANC initiation did not have an impact on NICU admission or PM. Future research on quality of ANC and barriers to ANC attendance would improve the scientific knowledge in the field.

8 Implications of the findings

This study identified a possible lack of proper classification and registration of stillbirths and ENDs; proper classification is vital for reliable statistics and subsequent analysis. The implementation of systematic autopsy in stillbirths and ENDs will improve knowledge about the causes of PM.

Multiparous women, younger and older women, women with lower education, and those who resided in rural areas tended to receive inadequate care, thus local and state health authorities should target these women as being at risk of receiving inadequate care. Public health interventions, educational campaigns, and understanding women's needs and expectations can be useful in reducing the number of women who receive inadequate care. Encouraging women to attend ANC as recommended may lead to a decrease in PM rates.

Further, restructuring the ANC programme based on low- and high-risk pregnancies and financing medically-initiated additional visits can be a step towards providing better quality care, because the adequacy of care is not the same for every woman, and the recommended number of ANC visits should be modified based on a woman's risk factors, personal characteristics, and reproductive health status. The number of visits outlined in ANC guidelines for uncomplicated pregnancies should be considered the minimum number required for proper risk management, with the first visits being longer and more comprehensive.

Finally, the present study highlighted the increasing potential of the GBR. Strengthening this system by improving its capacity, human resources, and technical support, is vital for better quality data, i.e., more reliable, consistent, and comparable information. An average of 52,000 women and newborn are registered in the system each year, and considerable data will be collected in the coming years. Therefore, our study showed the clear potential of the GBR to contribute to epidemiological research.

9 Further research

Epidemiological, registry-based studies on specific conditions during pregnancy, as well as separate analysis on low and high risk pregnancies would be helpful to identify modifiable risk factors of PM. Further, illustrating factors associated with PM by GA groups can improve the scientific knowledge on contributor factors to high PM rates in Georgia. Quantitative studies on causes on preterm birth and NICU admission will complement our findings.

To display the broader picture and identify the barriers to adequate ANC, further qualitative research is essential. Research questions that could be asked include geographical and financial accessibility, as well as women's expectations of ANC, all of which can be considered exposures for adequate ANC, and can be addressed through well-structured questionnaires or interviews with randomly-selected women. Identifying personal, socioeconomic, and cultural barriers for initiating ANC and reasons for loss to follow-up is the next step in achieving a comprehensive understanding of the changes that are needed in the ANC programme and other public health interventions in Georgia.

On the other hand, complete and accurate information on maternal morbidity and preconception heath is vital, and reliable information on these variables is important. Missing autopsies is a limitation of research on cause of death and hopefully routine registration of placental histological findings can also help address pathophysiological concerns (153-155). Having this deeper analysis of each PM case would expand the knowledge of causes and exact time of death.

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Appendix 1.

The criterion of the main causes of ENDs based on Wigglesworth classification.

Congenital malformation	Lethal congenital malformations (ICD-10 codes: Q00-Q05, Q20-Q25 (most common), Q33, Q39, Q41, Q42, Q61, Q74-Q79, and Q87-Q89).
Birth asphyxia	birth asphyxia and GA >27 weeks or weight >1000 g ischemic encephalopathy Apgar score <7
Prematurity	Respiratory distress syndrome and GA <37 weeks Birth asphyxia and GA <27 weeks or weight <1000 g Infection with GA <33 weeks
Infection	Infection and GA >33 Sepsis, meningitis
Other	Respiratory distress syndrome and GA ≥37 Meconium aspiration syndrome All others

GA: gestational age

Paper I

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Research Article

Incidence and Causes of Perinatal Mortality in Georgia

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ABSTRACT

Georgia has one of the highest perinatal mortality rates (i.e., stillbirths and early neonatal deaths combined) in Europe. The Georgian Birth Registry was started in 2016 to provide data for preventive measures of maternal and child health. In this study, we aim to determine the incidence of perinatal mortality, assess the distribution of stillbirths and early neonatal deaths, and to determine the major causes of perinatal mortality in Georgia. Data sources were the Georgian Birth Registry and the vital registration system for the year 2017. Causes of early neonatal deaths were assigned into five categories, using the Wigglesworth classification with the Neonatal and Intrauterine deaths Classification according to Etiology modification. The study used descriptive statistics only, specifically counts, means, proportions, and rates, using the statistical software STATA version 15.0 (StataCorp, College Station, TX, USA). In 2017, 489 stillbirths and 238 early neonatal deaths were recorded, resulting in a perinatal mortality rate of 13.6 per 1000 births. About 80% of stillbirths had an unknown cause of death. The majority of stillbirths occurred before the start of labor (85%), and almost one-third were delivered by caesarean section (28%). Prematurity (58%) and congenital malformations (23%) were the main causes of early neonatal deaths, and 70% of early neonatal deaths occurred after the first day of life. The perinatal mortality rate in Georgia remained high in 2017. The major causes of early neonatal deaths were comparable to those of many high-income countries. Contrary to global data, most early neonatal deaths occurred after the first day of life.

1. INTRODUCTION

Significant improvement in child survival has been achieved worldwide over the past 25 years. The mortality rate for children under the age of 5 years decreased from 91 deaths per 1000 livebirths in 1990 to 43 per 1000 in 2015 [1,2]. Death during the first month of life (the neonatal period) accounts for around 45% of mortality among children under the age of 5 years. Of those deaths, the majority (≈75%) occurs during the first 7 days of life (the early neonatal period) [3–5], and >50% occur during the first 24 hours [3,6,7]. Thus, the early neonatal period is the most critical time for an infant [2]. Since 2000, stillbirth rates have decreased by 25% globally [8], but there are still large disparities between countries [9].

The combined measure of stillbirths and early neonatal deaths (ENDs) comprises perinatal mortality (PM) [10]. Stillbirth is defined as the delivery of a fetus born with no signs of life. However, the definition varies across countries by gestational age and birthweight, which complicates international comparisons [11]. Georgian national guidelines define stillbirth as a fetus born with no sign of life at 22 completed gestational weeks or more, or a birthweight of >500 g, if the gestational age is unknown.

The causes of PM are numerous and vary according to the health status of the mother and access to antenatal care. About 99% of PM occurs in low- and middle-income countries [12]. In areas where pregnant women have access to quality healthcare services, congenital malformations, preterm birth, and intrauterine growth restriction are the leading causes of PM. In areas with low healthcare service coverage, the main causes of PM are asphyxia, neonatal tetanus, and infections [13]. Comparing specific causes of stillbirth is a challenge as a universal worldwide classification of causes of stillbirth is missing [11,14,15].

Georgia is a lower middle-income country with 3,729,600 inhabitants and has one of the highest PM rates in Europe [16–18]. In 2016, the fertility rate was 2.24, and the total birth rate was 15.2 per 1000 total population. Since 2001, the rate of stillbirths has decreased by 36%, but then stagnated, reaching 9.8 per 1000 total births in 2016 [17]. In 2016, the neonatal mortality rate was 6.3 and the END rate was 4.1 per 1000 livebirths, a slight increase from 3.8 in 2015. By the end of 2030, Georgia aims to reduce neonatal mortality to 5 per 1000 livebirths and the stillborn rate to 6.8 per 1000 total births [19]. To reach these goals, it is crucial to investigate the causes and characteristics of stillbirths and ENDs.

Until 2017, all births and deaths in Georgia were registered in a vital registration system (VRS) administered by the Ministry of Justice. In 2017, this responsibility was transferred to the National Centre for Disease Control and Public Health (NCDC). In 2016, the Georgian Birth Registry (GBR) was established, a digital medical birth registry with national coverage. Maternity homes are obliged to notify the Ministry of Health, the NCDC, and the GBR of all stillbirths and neonatal deaths within 24 h. Details on

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the implementation of the GBR are described elsewhere [20]. This study aims to determine the incidence of PM, assess the distribution of stillbirths and ENDs, and determine the major causes of PM in Georgia in 2017.

2. MATERIALS AND METHODS

2.1. Study Population

We extracted all cases of PM reported in the GBR and VRS in 2017. Information from the two databases was merged by the unique personal identification numbers of newborns and mothers. Any additional information identified in the VRS was used as supplemental data. In total, 52,228 mothers and 52,961 newborns were registered in the GBR in 2017. This corresponds to 98.5% of the newborns registered in the VRS. We excluded mothers with parity >15 (n = 14) and aged <13 or >53 years (n = 2), as well as newborns with a gestational age >43 weeks (n = 2) and a birthweight <100 g (n = 30), (gestational age was known for all newborns, but we excluded those with biologically implausible values). Twin births were included in the study for description of all PM cases in Georgia. Thus, the final study population included 52,180 mothers and 52,913 newborns, of which 489 were registered as stillbirths (gestational age ≥22 weeks) and 148 as ENDs. Sixty-six additional ENDs were identified in the VRS as newborns who die at home or after transfer to another hospital were not be registered as PM in the GBR. Thus, the total number of cases of PM was 729 in 2017. When considering causes of death for stillbirths and ENDs, we excluded ENDs with missing personal identification number (n = 24), as they could not be merged with GBR data. As the VRS registers all births and deaths in the country, we validated the PM cases through the VRS using maternal and personal identification number. The gestational age variable at delivery was validated using self-reported last menstrual period and gestational age at different antenatal care visits throughout pregnancy.

2.2. Study Setting

In Georgia, the majority of pregnant women use antenatal care services and 81% attend at least four visits [16]. Almost all (99.8%) give birth at government-approved medical centers assisted by gynecologists (of which there are 50 per 100,000 population) [16]. Pregnant women may attend four antenatal care visits free of charge under the national universal health coverage program. In 2016, >270 antenatal care centers and maternity hospitals provided services and reported to the GBR [16]. The doctors or other trained medical personnel in the maternity wards and antenatal care centers feed information on each pregnancy, delivery and newborn in the GBR.

2.3. Assigning Causes of Death

The GBR and VRS register causes of death according to the International Statistical Classification of Death and Related Health Problems 10th revision (ICD-10). However, whereas in the GBR, there is no limit either on the number of causes of death that can be registered or on any of order of events; the VRS defines primary cause and up to three underlying causes of death. Moreover, only the GBR provides cause of death for stillbirths as these causes are not registered in the VRS. Therefore, GBR was the primary source for all stillbirth causes of death. For ENDs, we compared the ICD-10 codes for causes of death in the GBR with those in the VRS and found 90% complete agreement. However, in 10% of cases, the VRS was either more comprehensive, or included the ICD-10 code for congenital malformation. Therefore, if newborns had a lethal congenital malformation in the VRS or in the GBR, they were assigned to the congenital malformation group.

When assigning a primary cause of death to ENDs, we used the Wigglesworth classification with the Neonatal and Intrauterine deaths Classification according to Etiology modification [21,22], which is based on birthweight, gestational age, Apgar score after 5 min, presence of lethal congenital malformation, causes of death (extracted from the GBR and VRS), and the underlying causes of death (extracted from the VRS). All recorded causes of death for each END case were listed together with the other aforementioned variables in order to assign one of the following causes of death: preterm delivery, congenital malformations, birth asphyxia, infection, and others. Appendix 1 summarizes criteria for assigning case-specific cause of death.

2.4. Statistical Analysis

Descriptive statistics were used for continuous variables as means and for categorical and dichotomous variables as percentages. The data were analyzed using the statistical software STATA version 15.0 (StataCorp, College Station, TX, USA).

2.5. Ethical Consideration

The NCDC Institutional Review Board revised and approved the study protocol (IRB # 2017-010 31.03.2017). Moreover, the Regional Committee for Medical and Health Research Ethics, North Norway, approved the use of the data from the GBR for research purposes (2017/404/REK Nord) [20].

3. RESULTS

In 2017, the PM rate was 13.6 per 1000 total births, and stillborn and END rates were 9.1 per 1000 total births and 4.5 per 1000 livebirths, respectively. The ratio of stillborn to ENDs was 2.1, and the proportion of ENDs to total number of neonatal deaths was 0.66. The majority of stillbirths (415, ≈85%) died antepartum, whereas only 45 (9%) were reported as intrapartum stillbirths. The remaining stillbirths (6%) had an unknown time of death. Of 214 ENDs, 64 (≈30%) died within the first 24 h, 65 (30%) between 24 and 72 h, and 85 (≈40%) between 73 and 168 h. The majority of stillbirths and ENDs occurred among extremely preterm newborns (gestational age 22–27 weeks), whereas 23% of stillbirths and 17% of ENDs were born at term (Table 1).

Mean gestational age and birthweight were 30.6 weeks and 1569 g in stillbirths, and 29.9 weeks and 1490 g among ENDs, which was significantly lower than the values in livebirths (38.6 weeks; 3264 g). In all, 28% of stillbirths and 58% of ENDs were delivered

Table 1 Number of stillbirths, early neonatal deaths (ENDs), perinatal mortality (PM) cases, and total births in Georgia in 2017 by gestational age (GA)

GA, weeks	Stillbirths, *n* (%)	ENDs, *n* (%)	PM, *n* (%)	Total births, *n* (%)
22–27	189 (38.6)	82 (38.3)	271 (38.6)	545 (1)
28–31	87 (17.8)	67 (31.3)	154 (21.9)	559 (1.1)
32–36	99 (20.3)	29 (13.6)	128 (18.2)	3511 (6.6)
≥37	114 (23.3)	36 (16.8)	150 (21.3)	48,298 (91.3)
All	489	214	703	52,913

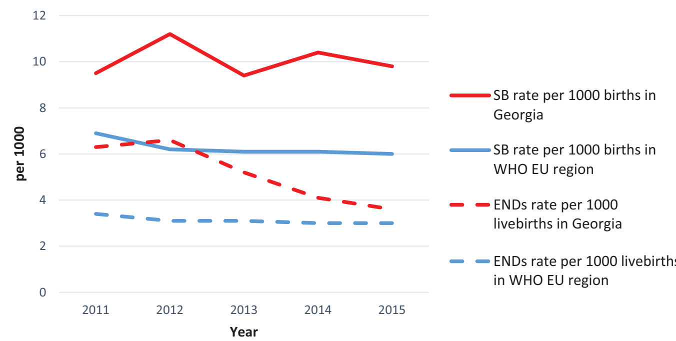

Figure 1 The rates of stillbirth (SB) and early neonatal deaths (ENDs) in Georgia and in World Health Organization European (WHO EU) region.

by caesarean section. Furthermore, 2.3% of stillbirths and 23.0% ENDs were diagnosed with congenital malformations, which was significantly higher than that in livebirths (0.4%).

The majority of stillbirths were registered with an unknown cause of death (80%). The most commonly reported causes of death for stillbirths were maternal conditions (7.8%) and complications of the placenta and the umbilical cord (5.2%). Congenital malformations were registered in 2.6% of stillbirths. There was no missing information on the cause of death for ENDs. The leading cause of death in this group was preterm delivery (58%), followed by congenital malformations (23%), birth asphyxia (7%), and infections (7%). However, the cause of death for ENDs changes by gestational age, with preterm delivery being most common (89%) cause at a gestational age of 22–27 weeks, whereas congenital malformation was the leading cause of death after 32 weeks of gestational age (Table 2).

4. DISCUSSION

This study confirms that the PM rate (13.6 per 1000 births in 2017) in Georgia is higher relative to most other European countries, except for Armenia [18]. In 2015, the World Health Organization (WHO) reports an average PM rate of 8.9 per 1000 total births in Europe; in the Commonwealth of Independent States the value is 11; in members of the European Union it is 6.5; and in the Nordic countries it is 5 (Figure 1) [18]. The differences in stillbirth rates are much greater than those in END rates. Consequently, stillbirths contribute much more to the PM rate in Georgia than in the WHO European region.

An important finding in the present study is that 70% of ENDs died after the first 24 h of life. This is very different to what was recently reported worldwide, where the majority (50–65%) of newborns die within the first 24 h of life, and the number of newborn deaths decrease with time since birth [3,7,23]. In addition, the proportion of stillbirths delivered by caesarean section was quite high in our study (≈28%), although national guidelines recommend vaginal delivery in these cases. Together these findings may indicate misclassification of ENDs as stillbirths.

The WHO published country-specific, regional and global estimates based on the different countries' level of development, and Georgia was estimated to have a ratio of stillborn to ENDs of 1.2 [24]. However, the data from the GBR suggest that this ratio is almost twice that high, which again may indicate misclassification of ENDs as stillbirths. Furthermore, the ratio of ENDs to total neonatal deaths was 0.66 for Georgia in 2017, and the average value for Western European countries was 0.77, with few values below 0.7 [2], which suggests that the proportion of ENDs in the PM rate is lower than expected.

In high-income countries, stillbirth rates vary from 1.3 to 8.8 per 1000 total births, clearly indicating the potential for prevention in Georgia having a stillbirth rate 9.1 per 1000 births. Only four countries (Greece, Hungary, Portugal, and the United Kingdom) in Europe use a different definition of stillbirth (fetus born with no sign of life after 24 weeks of gestation). Thus, data from all other European countries are directly comparable to ours.

Previous studies have shown that more than one-third of all stillbirths occur during labor [8,24], and that intrapartum stillbirths are more common in low-income countries. Our results are not in line with these findings, as intrapartum deaths comprised only 9% of stillbirths. This finding also supports the idea about misclassification of intrapartum deaths and ENDs as stillbirths, and in addition may suggest disparities in quality of obstetric practice.

Our results show that 80% of stillbirths were registered with an unknown cause of death. Compared with other countries, this proportion is high. Indeed, previous studies reported an unknown

Table 2 Causes of early neonatal death (END) according to Wigglesworth classification with Neonatal and Intrauterine deaths Classification according to Etiology modification stratified by gestational age (GA)

	Total ENDs, *n* = 214, *n* (%)	GA = 22–27, *n* = 82, *n* (%)	GA = 28–31, *n* = 67, *n* (%)	GA = 32–36, *n* = 29, *n* (%)	GA ≥ 37, *n* = 36, *n* (%)
Preterm delivery	123 (58)	72 (88)	48 (72)	3 (10)	0
Congenital malformation	50 (23)	9 (11)	14 (21)	13 (45)	14 (39)
Birth asphyxia	15 (7)	1 (1)	3 (4)	5 (17)	6 (17)
Infection	15 (7)	0	2 (3)	6 (21)	7 (19)
Other	11 (5)	0	0	2 (7)	9 (25)

cause of death in 32% of stillbirths in high-income countries and 43% in middle-income countries [25–27]. Possible explanations may be the high proportion of reported antepartum stillbirths (85%), incomplete input of information into the GBR about stillbirths, and the fact that few autopsies are done in Georgia as autopsy is not required by law.

In line with previous studies, preterm delivery (58%) and congenital malformations (23%) were the leading causes of ENDs in Georgia [3,21,26,28]. Whereas preterm mortality was most common at low gestational ages, the proportion of congenital malformation increased with increasing gestational age and was the most frequently occurring cause of death among ENDs born at a gestational age of 32–36 weeks, as reported by others [29,30]. It is noteworthy that the prevalence of congenital malformation among newborns who survived beyond the seventh day of life was very low (0.4%) compared with Norway (3.7%) [31]. As nonlethal malformations detected after hospital discharge are not added to the GBR, the incidence of congenital malformations is low.

Perinatal mortality and stillborn rates are higher in Georgia than in most high-income countries, but the leading causes of ENDs were similar. In low- and middle-income countries, 25% of ENDs are usually attributable to asphyxia, whereas in Georgia, asphyxia was attributed to only 7% of ENDs [3,32]. The low proportion of ENDs attributable to asphyxia also support the notion that some ENDs may be classified as stillbirths. Other studies have also confirmed that ENDs are often misclassified as stillbirths, or are underreported in low-income countries [3]. In fact, disparities in the time of death for ENDs, causes of death for both stillbirths and ENDs, and stillborn to END ratios in this study may be explained by misclassification of asphyxiated ENDs as stillbirths. This practice of reporting has been demonstrated previously [33,34]. Such misclassification increases the stillbirth rate, decreases the END rate, and changes the prevalence of causes of death in these groups. This possible selective reporting bias needs to be addressed in a validation study and in qualitative interviews with obstetric/pediatric professionals at different care levels in the Georgian healthcare system.

This study covers 98% of all officially reported PM cases in 2017, which is representative sample for Georgia. Another strength was the opportunity to merge the data from the GBR with that of the VRS, thereby validating reported cases across two independent reporting systems. Moreover, individual-level variables for each case were compared in the GBR and VRS to improve the completeness of reporting, validity of variables, and provide data for revision/defining underlying causes of death.

Nevertheless, the information in the GBR and VRS was not validated against medical records, which is a limitation. In addition, neither autopsy data nor placental histological examination were available, as these examinations are not routinely performed in Georgia; this complicates any search for the exact cause of death. The data to the GBR was transferred from medical files/records by the medical or administrative personnel, although the majority of them were properly trained, accidental misclassification could have occurred.

Future investigations of possible misclassification of ENDs as stillbirths are vital. Routine placental examinations and autopsies are recommended to identify causes of death, especially for those stillbirths who were delivered by caesarean section. More attention should also be given to birth asphyxia combined with intrapartum stillbirths, which is the main cause of death among children under 5 years of age, and which is largely invisible in healthcare policies [35]. Therefore, precise information about time of death and causes of PM will make it possible to detect knowledge gaps and provide data for further interventions.

5. CONCLUSION

Georgia has one of the highest PM rates (13.6 per 1000 births in 2017) in Europe. About 80% of stillbirths had an unknown cause of death, whereas the main causes of ENDs were preterm delivery and congenital malformations. Time of death for both stillbirths and ENDs differed from international data, which requires attention to details and integrity from the health personnel reporting to the GBR and VRS.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

T.M. coordinated data collection, performed statistical analysis, and drafted the first manuscript and revised it based on other authors' comments. C.R. conceptualized and designed data collection instruments, created the theoretical framework for the analysis, and critically reviewed the manuscript. F.E.S. conceptualized and oversaw the study, and critically reviewed the manuscript. N.K. designed the study, and critically reviewed the manuscript. E.E.A. conceptualized, designed, and oversaw the study, and critically reviewed the manuscript. All authors contributed to the interpretation of the data, reviewed the draft of manuscript, and approved the final version submitted for publication.

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ABBREVIATIONS

PM, perinatal mortality; END, early neonatal death; GBR, Georgian Birth Registry; VRS, vital registration system; NCDC, National Centre for Disease Control and Public Health; ICD-10, International Statistical Classification of Death and Related Health Problems 10th revision; CS, caesarean section; WHO, World Health Organization.

ETHICAL APPROVAL

The NCDC Institutional Review Board - protocol (IRB # 2017-010 31.03.2017). Regional Committee for Medical and Health Research Ethics of Northern Norway – approved the use of data from GBR for research purposes (2017/404/REK Nord).

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APPENDIX 1

Summary of criteria for assigning case-specific cause of death for ENDs.

Congenital malformation	Lethal congenital malformation (ICD-10 codes: Q00–Q05, Q20–Q25 (most common), Q33, Q39, Q41, Q42, Q61, Q74–Q79, and Q87–Q89).
Birth asphyxia	Birth asphyxia and GA > 27 weeks or weight > 1000 g Ischemic encephalopathy Apgar score < 7
Prematurity	Respiratory distress syndrome and GA < 37 weeks Birth asphyxia and GA < 27 weeks or weight < 1000 g Infection with GA < 33 weeks
Infection	Infection and GA > 33 Sepsis, meningitis
Other	Respiratory distress syndrome and GA ≥ 37 Meconium aspiration syndrome All others

GA: gestational age.

Paper II

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ORIGINAL RESEARCH

Unattended Pregnancies and Perinatal Mortality in Georgia

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Introduction: The majority of pregnant women in Georgia attend the free-of-charge, national antenatal care (ANC) programme, but over 5% of pregnancies in the country are unattended. Moreover, Georgia has one of the highest perinatal mortality (PM) rates in Europe (11.7/1000 births).

Purpose: To assess the association between unattended pregnancies and the risk of PM.

Methods: Data were extracted from the Georgian Birth Registry (GBR) and the national vital registration system. All mothers who had singleton births and delivered in medical facilities in Georgia in 2017–2018 were included in the study and categorised into attended pregnancies (at least one ANC visit during pregnancy) and unattended pregnancies (no ANC visits during pregnancy). After exclusions, the study sample included 101,663 women and their newborns, of which 1186 were either stillborn or died within 7 days. Logistic regression analysis was used to assess the effect of unattended pregnancies on PM.

Results: During the study period, the PM rate was 12.9/1000 births. In total, 5.6% of women had unattended pregnancies. The odds of PM among women with unattended pregnancies were more than double those among women with attended pregnancies (odds ratio=2.21, [95% confidence interval: 1.81–2.70]). Multiparous women with higher education and who resided/delivered outside of Tbilisi were significantly less likely to experience PM.

Conclusion: The risk of PM doubled among women with unattended pregnancies. Six percent of PM cases were attributable to unattended pregnancies. Targeting women with previous unattended pregnancies will likely reduce the PM rate in Georgia.

Keywords: stillbirth, early neonatal mortality, antenatal care, birth registry

Introduction

The availability of antenatal care (ANC) and subsequent ANC attendance by pregnant women have an influence on pregnancy outcomes. ANC improves maternal and newborn survival because it reduces the risk of preterm birth and perinatal mortality (PM)[1–4] through individual risk assessment and monitoring. In both high- and low-income countries, associations between lack of ANC attendance and adverse pregnancy outcomes have been demonstrated.[2] Thus, it is important to identify women who never attend ANC in order to prevent severe morbidity and mortality during pregnancy or delivery.

The Auckland Stillbirth Study showed that the odds of stillbirth doubled among women who attended less than half of the recommended ANC visits.[5] A study from Saudi Arabia found a 70% increased risk of intra-uterine foetal death in women who did not attend ANC,[6] and a systematic literature review from low- and middle-income countries reported that lack of ANC attendance was one of the main factors

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associated with stillbirth.[7] Additionally, a study from Bangladesh showed that women who attended ANC were 18% less likely to experience early neonatal death (END) when compared to those who did not attend ANC.[8] Dowswell et al compared the effect of reduced ANC attendance and standard care among women with low-risk pregnancies, and found that women with reduced ANC attendance had a 14% increased risk of PM compared to those in the standard care group. Furthermore, in low- and middle-income countries, the PM rate was significantly higher among women who did not attend the recommended number of ANC visits.[9] Previous research has suggested that lack of ANC visits also increases the risk of preterm birth by up to 30%.[10] When small for gestational age (GA) newborns were not identified prior to birth, their odds of being stillborn were 9.46 times higher than those of small for GA babies that were identified during the antenatal period.[5] Small for GA and preterm birth are recognised as the main contributors to PM.[11,12] Although many studies have investigated the associations between recommended ANC visits and PM, very few have assessed the effect of unattended pregnancies.

Prior to 2018 in Georgia, the national ANC programme covered four ANC visits per woman, free of charge.[13] On 1 February 2018, this number was increased to eight, as recommended by the World Health Organisation.[14] In 2017–2018, the proportion of women attending at least four ANC visits in Georgia increased by 4.5%, thus reaching a total of 80.8% based on the aggregated data from medical facilities in the country.[15] However, little is known about maternal and neonatal outcomes among women who do not attend ANC in Georgia.

The aims of this paper are to identify the characteristics of women with unattended pregnancies in Georgia, to assess the association between unattended pregnancies and the risk of PM, and to measure the burden of PM attributable to unattended pregnancies.

Methods

The Georgian Birth Registry

The Georgian Birth Registry (GBR) was established in 2016 as a digital, medical birth registry with national coverage. Doctors or other qualified medical personnel record all pregnancies, related ANC visits, and maternal health conditions arising before, during, and after pregnancy. Moreover, all ANC centres, including those without maternity wards (n=350), are obligated by law to register any ANC visit (state financed or private) in the GBR, and all stillbirths reported by the National Statistics Office of Georgia are also registered.

Study Population

For the present analysis, we extracted maternal and neonatal data (including stillbirths) for all deliveries occurring in 2017–2018. Confirmed END cases were extracted from the vital registration system (VRS), as the GBR does not register neonatal outcomes that occur after hospital discharge or during transfer to other facilities. GBR and VRS data were merged using mothers' and newborns' unique 11-digit personal identification number (issued at time of birth). Thirty-eight ENDs without either the mother's or the newborn's personal identification number were excluded from the analysis.

During the study period, there were 103,128 mothers and 104,597 newborns registered in the GBR. We excluded multiple births (n=2911) because they have a higher risk of preterm birth, complications during pregnancy and PM than singletons. Biologically implausible values and outliers: parity (>15; n=13); age (>53 years; n=8), and newborns with a GA of >43 weeks (n=2). The final study sample comprised 101,663 mothers and newborns. Among those, we identified 1186 PM cases (658 from 2017 and 528 from 2018) (Figure 1).

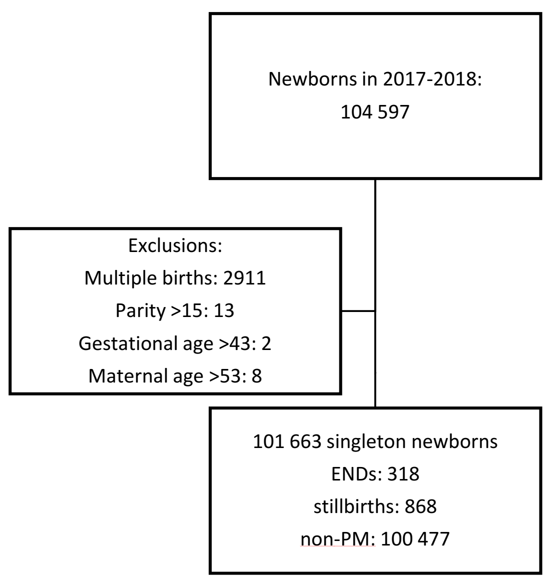

Figure 1 Flow chart of the study sample.

Included Variables

Information on ANC attendance in the GBR was used to categorise mothers into two groups: attended pregnancies (women who attended at least one ANC visit during pregnancy) and unattended pregnancies (women who did not attend any ANC visits during pregnancy). We also included maternal age (≤19, 20–24, 25–29, 30–34, 35–39, ≥40 years), parity (primiparous, multiparous), and education (primary, secondary, and higher). The variable "region of residence and delivery" was combined: resided and delivered in Tbilisi (capital); resided in Tbilisi and delivered outside Tbilisi; resided outside Tbilisi and delivered in Tbilisi; and resided and delivered outside Tbilisi.

Statistical Analysis

Descriptive statistics are presented as means and standard deviations for continuous variables and percentages for categorical variables. We used logistic regression analysis to assess the effect of ANC attendance (attended and unattended pregnancies) on PM. To determine which covariates to include in the regression model, we drew a directed acyclic graph (DAG), including ANC, PM, GA, and the following maternal factors: morbidity, age, parity, education, region of residence and delivery, nationality, marital status, and year of delivery (Figure 2). The DAG assumed a causal effect of ANC on PM, as indicated by the direct arrow from ANC to PM.[16–18]

We assumed that ANC attendance affected GA. Indeed, if a woman has an unattended pregnancy, the risk of early delivery due to medical conditions cannot be recognised, and thus cannot be avoided. If a woman has an attended pregnancy, and for some reason the doctor plans to perform a caesarean section at a particular date, this also affects GA. We further assumed that the maternal factors age, parity, education, and region of residence and delivery affected ANC attendance and increased the risk of PM through GA. Previous research has also highlighted the importance of these variables in ANC attendance.[1,8,19,20] Thus, these variables can be considered confounders in the causal pathway between ANC attendance and PM. Maternal morbidity increases the risk of PM and affects GA; however there is no direct effect of maternal morbidity on ANC attendance, or vice-versa. The maternal factors nationality, marital status, and year of delivery have an effect on ANC, but they have no direct effect on PM. As there are three arrows pointing at GA, it becomes a collider; as conditioning on a collider introduces bias,[17,21] we did not adjust for GA in our regression model.[18,21,22] Thus, based on the DAG, the regression model was adjusted for the following maternal factors: age, parity, education, and region of residence and delivery, to properly assess the effect of ANC attendance on PM. Other studies adjusted for similar variables, with some modifications.[1,5,6,8]

To estimate the burden of PM attributable to unattended pregnancy, we calculated the population attributable fraction (PAF) using the PUNAFCC Stata package, under the

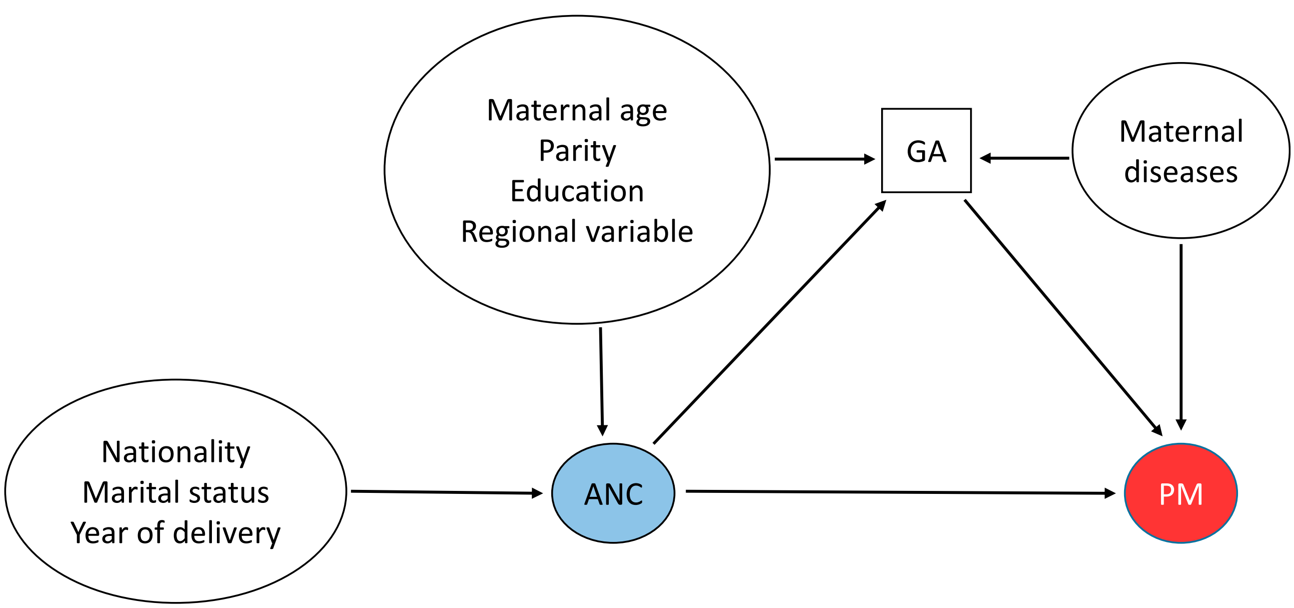

Figure 2 Directed acyclic graph presenting causal associations between perinatal mortality (PM), antenatal care (ANC) attendance, and potential confounders. GA: gestational age.

assumption that there is a causal effect of ANC attendance on PM. PAF is defined as the fraction of all cases of a disease or condition in a population which is attributable to the exposure.[23] As the GBR contains almost every birth in Georgia and is representative of the whole population, the current study gave us the opportunity to calculate PAF. Statistical analysis was performed using the statistical package STATA (StataCorp, College Station, TX, USA) version 15.0.

Results

The birth rate was 13.7 (95% confidence interval [CI] 13.-6–13.8) per 1000 population and the PM rate was 12.9 (95% CI 12.2–13.6) per 1000 births. Stillborn and END rates were 9 (95% CI 8.4–9.6) per 1000 births and 3.9 (95% CI 3.6–4.3) per 1000 livebirths, respectively. Thus, the ratio of stillbirths to ENDs was 2.3. In our study, the proportion of preterm newborns was 8.6%. In total, 5.6% of women had unattended pregnancies. Figure 3 displays the PM rate by GA for attended and unattended pregnancies.

The PM rate among women with attended pregnancies in our study sample was 10.7 per 1000 births (95% CI 10.8–12.1), whereas the PM rate among those with unattended pregnancies was 28.7 per 1000 births (95% CI 25.9–34.7) (Table 1). Women who experienced PM were older, less educated, and resided outside Tbilisi but delivered in Tbilisi compared to women who did not experience PM. The mean birthweight and GA of PM cases were lower than those of non-PM cases (Table 2).

Most women with unattended pregnancies were 25–29 years old (29%), multiparous (69%), had secondary education (44%), and resided and delivered outside of Tbilisi (52%). Compared to women with attended pregnancies, a higher proportion of women with unattended pregnancies were aged <19 or >35 years and multiparous, whereas the other characteristics were comparable between the two groups.

The mean birthweight (3154 g) and mean GA (38^{+1} weeks) was lower among women with unattended pregnancies compared to those with attended pregnancies (birthweight: 3278 g, GA: 38^{+4}) (Table 3). Additionally, women from Armenia and Azerbaijan were less likely to seek ANC than Georgian women: 6% of Armenians and 11% of Azerbaijanis had unattended pregnancies, compared to 3.7% of Georgian women. There was a disparity in ANC attendance across regions, with women residing in the regions of Kakheti, Samegrelo and Zemo Svaneti, Mtskheta-Mtianeti, and Abkhazia having a higher than average rate of unattended pregnancies (Figure 4).

After adjustments for maternal age, parity, education, and region of residence and delivery, women with unattended pregnancies had more than two times higher odds of experiencing PM, compared to women with attended pregnancies (odds ratio [OR]=2.21, [95% CI 1.81–2.70]). Increased maternal age was strongly associated with PM, with women aged ≥40 years had more than three-fold higher odds of experiencing PM (OR=3.50, [95% CI 2.78–4.42]) compared to women aged 25–29 years. Primiparous women were 43% more likely to experience PM, compared to multiparous women (OR=1.43, [95% CI 1.25–1.63]). Maternal education was inversely associated with PM (higher vs secondary, OR=0.56, [95% CI 0.48–0.65]). Women who resided

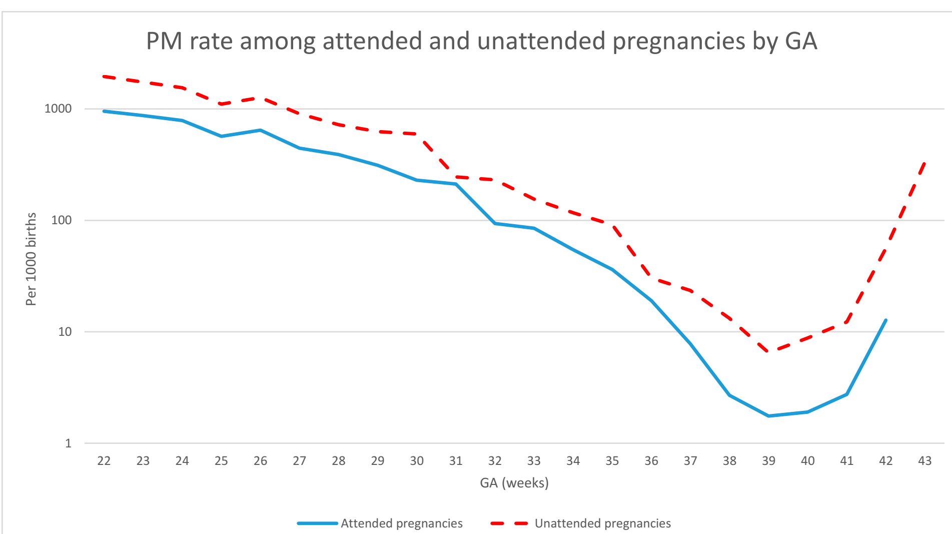

Figure 3 Perinatal mortality (PM) rate by gestational age (GA) and ANC attendance (attended pregnancies: at least one ANC visit during pregnancy; unattended pregnancies: no ANC visits during pregnancy) among singletons.

Table 1 Incidence of Early Neonatal Death (END), Stillbirth (SB), and Perinatal Mortality (PM) by Antenatal Care Attendance (Attended and Unattended Pregnancies[a]).

	Attended Pregnancies N=95,957 (94.4%)	Unattended Pregnancies N=5706 (5.6%)
Incidence of		
END (per 1000 livebirths), n	2.9 (276)	7.5 (42)
SB (per 1000 births), n	7.8 (746)	21.4 (122)
PM (per 1000 births), n	10.7 (1022)	28.7 (164)

Notes: [a]Attended pregnancies: at least one ANC visit during pregnancy; unattended pregnancies: no ANC visits during pregnancy.

outside of the capital, Tbilisi, but delivered in Tbilisi had 93% higher odds of experiencing PM compared to women who resided and delivered in Tbilisi (OR=1.93, [95% CI 1.63–2.29]) (Table 4). If women with unattended pregnancies had attended at least one ANC visit, 5.9% (4.9–6.9%) of PM cases could have been avoided, which translates into 71 singleton PM cases in 2017–2018.

Discussion

In this register-based study of 101,663 women from Georgia who delivered singleton newborns, we found that women with unattended pregnancies (ie, who did not attend any ANC visits), had more than two times higher odds of experiencing PM when compared to those with an attended pregnancy (ie, those who attended at least one ANC visit). Older maternal age, primiparity, primary education, and residing outside and delivering in Tbilisi increased the odds of PM, whereas higher education, multiparity, and residing and delivering outside of Tbilisi were associated with reduced odds of PM. Assuming a causal effect of ANC non-attendance on PM, we estimated that almost 6% of singleton PM cases in Georgia could have been avoided if the mothers had attended at least one ANC visit.

Our results suggested that unattended pregnancy increases the odds of PM, which is in line with prior studies that have demonstrated the importance of ANC with regard to PM.[9,24,25] Earlier research showed that missing attendance or lack of ANC had a strong impact on the risk of stillbirth[5–7] and END.[8] Moreover, lack of ANC was strongly associated with the risk of preterm birth and small for GA newborns,[5,10] both of which are main contributors to PM.[11,12] The coverage of at least one ANC visit differed by region of residence, which might be partially explained by the geographical distribution of

Table 2 Maternal and Neonatal Characteristics by Singleton Perinatal Mortality (PM) Cases.

	PM Cases N=1186	Non-PM Cases N=100 477
Maternal Age, % (n)	% (n)	% (n)
≤19	3.4 (40)	3.6 (3545)
20–24	18.5 (219)	23 (23,078)
25–29	25.6 (304)	32.8 (32,941)
30–34	22.3 (264)	24 (24,224)
35–39	19.6 (233)	12.6 (12,676)
≥40	10.6 (126)	4 (4013)
Parity, % (n)[a]		
Primiparous	40.6 (481)	38.3 (38,476)
Multiparous	59.4 (705)	61.7 (61,963)
Education, % (n)		
Primary	10.3 (122)	8.3 (8362)
Secondary	50.4 (598)	46.3 (46,538)
Higher	28.1 (333)	36.1 (36,288)
Unknown	11.2 (133)	9.3 (9289)
Regional, % (n)[b]		
Resided and gave birth in Tbilisi	30.1 (357)	33.1 (33,251)
Resided in Tbilisi and gave birth outside of Tbilisi	1.3 (15)	0.9 (903)
Resided outside of Tbilisi and gave birth in Tbilisi	24.5 (291)	13.9 (13,971)
Resided and gave birth outside of Tbilisi	44 (522)	52 (52,268)
Weight mean (SD)	1594 (1093)	3291 (516)
Gestational age week mean (SD)	30^{+4} (5.9)	38^{+4} (1.7)

Notes: [a]38 missing, [b]85 missing.
Abbreviation: SD, standard deviation.
The Georgian Birth Registry 2017–2018.

maternity hospitals and ANC centres in the country. Based on the perinatal regionalisation programme, all level three hospitals, which provide the highest level of care and have neonatal intensive care units, are located in the regions of Tbilisi, Kvemo Kartli, Imereti, Adjara, and Kakheti. Moreover, the majority of all hospitals are situated in Tbilisi, Imereti, Adjara, and Kvemo Kartli. However, all other regions have a minimum of two hospitals, and some have more depending on the population size and the number of births. In this study, we showed that as many as 71 singleton PM cases could have been avoided during the 2-year study period if all women with singleton pregnancies attended ANC at least once. Thus, targeted efforts to increase ANC attendance among non-attending women could potentially save lives. Multiparous women from Azerbaijan or Armenia, women living and delivering outside of larger cities, and those with secondary education should be the primary audience for such interventions.

Table 3 Maternal and Neonatal Characteristics by ANC Attendance (Attended and Unattended Pregnancies[a]).

	Attended Pregnancies N=95,957 % (n)	Unattended Pregnancies N=5706 % (n)
Maternal Age, % (n)		
≤19	3 (3319)	5 (266)
20–24	23 (22,010)	22 (1287)
25–29	33 (31,563)	29 (1682)
30–34	24 (23,162)	23 (1326)
35–39	13 (12,086)	15 (823)
≥40	4 (3817)	6 (322)
Parity, % (n)[b]		
Primiparous	39 (37,182)	31 (1775)
Multiparous	61 (58,739)	69 (3929)
Education, % (n)		
Primary	8 (7744)	13 (740)
Secondary	46 (44,631)	44 (2505)
Higher	37 (35,407)	21 (1214)
Unknown	9 (8175)	22 (1247)
Regional, % (n)[c]		
Resided and gave birth in Tbilisi	33 (31,682)	34 (1926)
Resided in Tbilisi and gave birth outside of Tbilisi	1 (873)	<1 (45)
Resided outside of Tbilisi and gave birth in Tbilisi	14 (13,277)	17 (985)
Resided and gave birth outside of Tbilisi	52 (50,099)	48 (2691)
Weight mean (SD)	3278 (550)	3154 (659)
Gestational age week mean (SD)	38^{+4} (1.9)	38^{+1} (2.7)

Notes: [a]Attended pregnancies: at least one ANC visit during pregnancy; unattended pregnancies: no ANC visits during pregnancy. [b]38 missing, [c]85 missing
Abbreviation: SD, standard deviation.
The Georgian Birth Registry 2017–2018.

This study should also trigger future research to identify the reasons why women did not seek ANC.

In line with other studies,[26–28] the odds of PM increased with increasing maternal age, whereas higher education was negatively associated with PM. Moreover, primiparous women had higher odds of experiencing PM than multiparous women. In accordance with the present results, a meta-analysis of selected maternal and foetal factors for PM demonstrated an increased risk of PM among primiparous women; however, several other studies did not find a statistically significant association between parity and PM.[29] Additionally, women residing outside Tbilisi (the most populated city), but who gave birth in Tbilisi, had 93% higher odds of experiencing PM. This is reasonable, as many of these deliveries may have had complications that needed treatment at a level three hospital. These findings may be somewhat limited by internal migration, as people tend to move to larger cities.

The present study was designed to determine the effect of unattended pregnancies on PM, and one significant contributor to the outcome is GA at delivery. Thus, we plotted the relationship between GA and PM by ANC attendance, and the graph confirmed that the shape of the curve is comparable to that of other countries that have had systematic birth registration for many years.[22,30] The graph shows a PM rate that is similar across attended and unattended pregnancies before a GA of 36 weeks. After a GA of 37 weeks, the PM rate increased among women with unattended pregnancies. It is obvious that GA-specific PM rates differ by ANC attendance, and the PM rates among women with unattended pregnancies remained higher at all GAs. This figure confirms that the decision not to adjust for GA in our study was correct.

GA-specific PM is the focus of the Euro-Peristat project, which showed a wide variety in GA patterns of stillbirth and neonatal mortality in Europe.[31] In general, countries with low foetal mortality have a higher prevalence of foetal death at earlier GAs, while countries with high foetal mortality have higher percentages at and near term.[31] Georgia fits in the latter category; thus, the country's main concern is the PM cases delivered at a GA of 37–41 weeks, which comprised 21% of all PM cases in Georgia. The slight difference in mean GA between attended and unattended pregnancies can be explained by the high number of planned caesarean sections among women with attended pregnancies.

According to a study on differences in PM and infant mortality in high-income countries, the stillbirth to live-birth ratio among all newborns at GA 37–41 weeks is 0.1 in Finland, Iceland, and the US; and 0.2 in Denmark, Norway, Sweden, and Canada.[32] Our results showed that the same ratio was 0.3 in Georgia. Hence, the proportion of PM cases born at term might indirectly highlight the importance of ANC in the early identification of complications during pregnancy, and how this identification could improve perinatal outcomes[33] if proper treatment is provided during pregnancy or childbirth.

This study is the first attempt to determine the effect of unattended pregnancies on PM in Georgia. The main strength of this study is its substantial size, as it included nation-wide data from the GBR. Almost all women (99.8%) that delivered in Georgia during the study period were included in our analyses, which makes our study representative of the

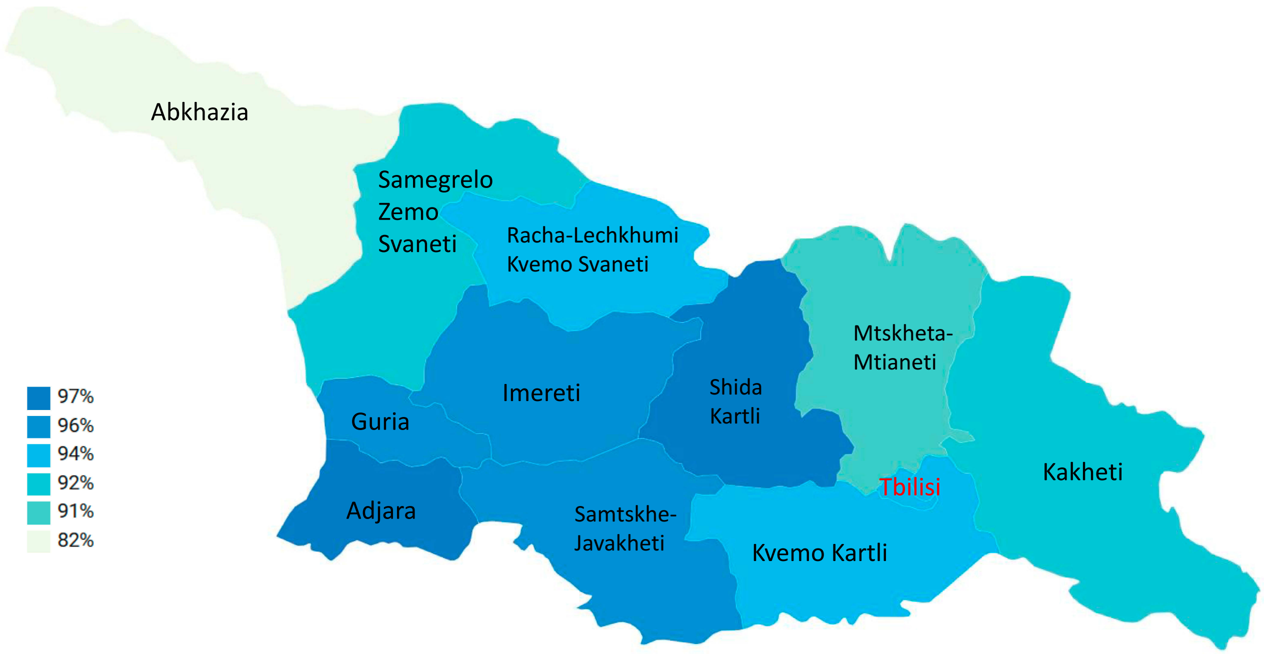

Figure 4 Map of Georgia – maternal residential regions by antenatal care attendance rates.

Georgian population. Another strength of the study is that the completeness, validity, and consistency of the GBR is ensured by a different registration system: the VRS; the GBR and the VRS represent two independent reporting systems with individual-level data. The number of mothers and newborns were validated by the VRS, which ensures the high coverage of the GBR. We were also able to validate the outcome of each pregnancy by merging the data from the GBR and the VRS.

We deliberately did not adjust our analysis for GA and maternal morbidity, because the aim of the study was to identify the overall effect of unattended pregnancies on PM, and we needed to adjust for maternal age, parity, education, and region of residence and delivery to block all backdoor pathways from PM to ANC. If our assumptions regarding the direction of the relationships between the included variables are wrong, our results may be biased. However, this is highly unlikely, as others have found similar associations between unattended pregnancies and PM, and most of the research adjusted for potential confounders.[5,9,24,25]

We were not able to validate the main exposure – unattended pregnancies –since the only data source for both public and private ANC attendance is the GBR. Thus, if there are women who had private ANC visits that were not registered, these women would have been misclassified in our analysis as unattended pregnancies. However, since ANC clinics and maternity houses are obligated by law to register ANC information in the GBR, we consider this unlikely, and thus that the proportion of women misclassified as having unattended pregnancies is very low.

Additionally, our findings may be somewhat limited as we did not take into account the causes of PM. In general 32–43% of stillbirths are due to unexplained causes in high- and low-income settings,[34] compared to 80% in Georgia. Unfortunately, we did not have the possibility to distinguish between preventable and inevitable causes of death.[35] In addition to the missing causes of stillbirth, the GBR contains incomplete information on morbidity during pregnancy. However, this fact does not undermine the importance of our main finding, which clearly identifies the importance of ANC with regard to PM in Georgia and suggests the value of increasing ANC attendance among women with previous unattended pregnancies.

Conclusion

Unattended pregnancy nearly doubled the odds of PM. Advanced maternal age, primiparity, and primary education also increased the risk of PM. The PAF of unattended pregnancies on PM was almost 6%; thus, an estimated maximum of 71 singleton PM cases would have been

Table 4 Odds Ratios and 95% Confidence Intervals for the Association Between Antenatal Care (ANC) Attendance (Attended and Unattended Pregnancies[a]), Maternal Characteristics, and PM.

Perinatal Mortality	Odds Ratio (95% Confidence Interval)
ANC Attendance	
Unattended pregnancy	2.21 (1.81 −2.70)
Attended pregnancy	1.0
Maternal Age	
≤19	0.72 (0.49–1.05)
20–24	0.87 (0.72–1.05)
25–29	1.0
30–34	1.34 (1.13–1.60)
35–39	2.19 (1.82–2.64)
≥45	3.50 (2.78–4.42)
Parity	
Primiparous	1.43 (1.25–1.63)
Multiparous	1.0
Education	
Primary	1.33 (1.08–1.63)
Secondary	1.0
Higher	0.56 (0.48–0.65)
Region of Residence and Delivery	
Resided and gave birth in Tbilisi	1.0
Resided in Tbilisi and gave birth outside of Tbilisi	1.49 (0.85–2.62)
Resided outside of Tbilisi and gave birth in Tbilisi	1.93 (1.63–2.29)
Resided and gave birth outside of Tbilisi	0.83 (0.72–0.98)

Notes: [a]Attended pregnancies: at least one ANC visit during pregnancy; unattended pregnancies: no ANC visits during pregnancy.

prevented in Georgia during the 2-year study period if all pregnant women had attended at least one ANC visit.

Policy and Practice Implications

Our study has important implications for ANC program development and future research. The major contribution of the present study is the illustration of the real effects of unattended pregnancies on PM in Georgia, as it provides actual numbers based on registry data. These numbers show that targeting women with previous unattended pregnancies could lead to a lower rate of unattended pregnancies and positively contribute to PM rates. Our results clearly underline the importance of ANC in Georgia for a better pregnancy experience. Strengthening family planning services, informing reproductive-age women about the ANC programme and about services covered by the government would also improve the rate of attended pregnancies. Finally, our study revealed several uninvestigated topics, including reasons for not attending ANC and barriers to pregnancy care, which we suggest should be the subject of future studies.

Ethics and Consent Statements

The NCDC Institutional Review Board revised and approved the study protocol (IRB # 2017-010 31.03.2017). The Regional Committee for Medical and Health Research Ethics, North Norway, approved the use of the data from the GBR for research purposes (2017/404/REK Nord).

Author Contributions

T.M. coordinated data collection, performed statistical analysis, drafted the manuscript and revised it based on other authors' comments. C.R. conceptualized and designed data collection instruments, created the theoretical framework for the analysis, and critically reviewed the manuscript. F. E.S. conceptualized and oversaw the study, and critically reviewed the manuscript. N.K. critically reviewed the manuscript. E.E.A. conceptualized, designed, and oversaw the study, and critically reviewed the manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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Paper III

Manjavidze, T., Rylander, C., Skjeldestad, F.E., Kazakhashvili, N. & Anda, E.E. The Impact of Antenatal Care Utilization on Perinatal Mortality and Admission to Neonatal Intensive Care Units in Georgia. (Submitted manuscript).

The impact of antenatal care utilization on admissions to neonatal intensive care units and perinatal mortality in Georgia

Original research

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NICU admission; perinatal mortality; antenatal care utilization; birth registry

Abstract

Introduction: Appropriate antenatal care (ANC) utilization has direct, significant effects on perinatal mortality (PM). Georgia has one of the highest PM rates (11.7 per 1000 births) in Europe and launched a more intensive ANC programme in 2018.

Aim: To evaluate the associations between the Adequacy of Prenatal Care Utilization (APNCU) index and neonatal intensive care unit (NICU) admission and PM in Georgia.

Methods: The Georgian Birth Registry (GBR), with linkage to the Vital Registration System, was used as the main data source; 148,407 eligible mothers and singleton newborns were identified during the observation period (2017-2019). The main exposure was ANC utilization, measured by the APNCU index, and the hospitalization registry was used to validate NICU admissions. Logistic regression analysis was used to assess the associations between the exposure and outcomes while controlling for potential confounders.

Results: The overall PM rate was 11.6/1000 births, and the proportion of newborns with a NICU admission was 7.8%. 85% of women initiated ANC before gestational age week 12. According to the APNCU index, 16% of women received inadequate, 10% intermediate, 38% adequate, and 36% intensive care. Women who received intermediate care had the lowest odds of PM (adjusted odds ratio [AOR]=0.56, 95% confidence interval [CI] 0.45-0.70), and newborns of women who received inadequate care had the highest odds of NICU admission (AOR=1.16, 95% CI 1.09-1.23) and PM (AOR=1.18, 95% CI 1.02-1.36).

Conclusion: ANC utilization is significantly associated with newborn asmissions to NICU and PM in Georgia. Women received inadequate care experienced the highest odds of newborn admissions to NICU and PM.

Introduction

Interventions before and during labour may reduce the risk of perinatal mortality (PM). Timely initiation of antenatal care (ANC) and attending ANC as recommended are the major strategic interventions available to improve newborn health outcomes. PM is strongly associated with maternal conditions like gestational diabetes, anaemia, hypertensive disorders, preterm labour, and intrauterine growth restriction [1], all of which can be identified and managed through proper ANC. Approximately 33% of stillbirths and 71% of neonatal deaths can be avoided if the coverage and quality of preconception care, ANC, and intrapartum care are improved [2]. Previous research has suggested that differences in PM across countries in the European Union could be explained by differences in the quality of ANC [3].

To be considered high quality, ANC must be initiated before gestational age (GA) week 12, and subsequent visits must be attended at recommended intervals throughout the pregnancy. In 2013, 58.6% of pregnant women globally attended ANC before GA week 12, but there were large regional variations [4]. Maternal education, socioeconomic status, healthcare access, family support, and previous pregnancy experience are recognized as major determinants of timely initiation of ANC. Less than three ANC visits was associated with increased risks of PM in Australia [5]. A study from the USA showed that the risk of preterm birth, stillbirth, early and late neonatal mortality increased as the number of ANC visits decreased [6].

Newborn admission to a neonatal intensive care unit (NICU) is another significant indicator of perinatal health. NICU admission and PM are related outcomes, since newborns are admitted to the NICU for severe medical conditions. More advanced medical technologies and better resource utilization may explain increases in newborn survival [7, 8]. Studies of women with low-risk pregnancies showed that, in limited-resource settings, reduced ANC visits did not have any effect on NICU admissions, but they were associated with an increase in PM [9]. Additionally, the risk of mortality or severe morbidity, which results in NICU admission, was two times higher for extremely preterm newborns whose mothers did not receive optimal ANC compared to those whose mothers did [10]. The delivery of high-quality ANC to women with high-risk pregnancies, including risk assessment and treatment with corticosteroids and magnesium sulphate, may reduce the risk of extremely preterm birth and NICU admission [11-13].

The adequacy of ANC utilization can be measured by several different indices, which take into account GA week at ANC initiation and the number of ANC visits adjusted for GA [14-17]. However, studies on ANC utilization suggest that results differ significantly by the indices used [17, 18]. For years, the Kessner index has been widely used to assess the association between ANC and birth outcomes [19, 20]. At the end of the 1990s, the Adequacy of Prenatal Care Utilization (APNCU) index was proposed as a better way of measuring ANC utilization [16]. The APNCU index is based on GA week at ANC initiation and the subsequent number of ANC visits. Studies using the APNCU index have identified associations between ANC utilization and small-for-GA newborns, preterm birth, and infant mortality [6, 21].

The recommendations for providing high-quality ANC have changed over time. In 2002, the World Health Organization (WHO) recommended goal-oriented, focused ANC: four ANC visits during pregnancy, with the first visit taking place before GA week 12. In 2016, the WHO changed its recommendation to eight ANC visits, of which six should take place in the third trimester, citing that as a better strategy for improving maternal, foetal, and neonatal outcomes [9, 22].

Georgia is an upper-middle income country with a population of 3.72 million. In 2018, the PM rate in Georgia was 11.7 per 1000 births [23], which is one of the highest among European countries. Additionally, a high proportion of women in Georgia attend at least four ANC visits during pregnancy (80.8%) [23], based on aggregated data from medical facilities. The proportion of women attending four ANC visits and initiating ANC before GA week 12 is increasing; however, these numbers are still far from Georgia's target of 100% by 2030 [24]. Our previous study showed that women who did not attend any ANC visits during pregnancy had two-fold higher odds of PM compared to women who attended at least one ANC visit [25].

To our knowledge, little is known about the relationship between adequacy of ANC utilization and NICU admission and PM, especially in countries with a relatively high PM rate. Additionally, the perinatal outcomes of different ANC groups remain uninvestigated in Georgia. The aims of this study were to evaluate the associations between the APNCU index and NICU admission and PM in Georgia.

Materials and methods

Study population

The Georgian Birth Registry (GBR) ensures registration of all medical facility-based deliveries and ANC visits. The coverage of newborns registered in the GBR is 99.8%; the remaining 0.2% are registration disparities between the GBR, civil registration, and home deliveries (which account for around 0.1% of all deliveries in Georgia) [23]. To supplement and validate GBR data, we used the Vital Registration System (VRS). The VRS registers all births and deaths in the country and is routinely used for GBR data validation. Without registering birth or death in VRS is it impossible to issue birth or death certificate, thus, a newborn cannot have a personal identification number and diseased person cannot be buried. It means that all births and death in the country (except very minor exceptions) are registered in the VRS. Outcomes for transferred or discharged newborns are not sufficiently registered in the GBR, thus VRS data is used to identify cases of early neonatal death (END) (including time of birth and death).

From January 1st 2017 to December 31st 2019, 152,798 newborns and 150,593 mothers were registered in the GBR. After merging GBR and VRS data, we identified 1396 stillbirths (GBR) and 537 ENDs (VRS). We excluded 41 cases of ENDs which had a missing newborn and/or maternal ID. We also excluded multiple births (n=2163), due to the higher risk of complications during pregnancy and delivery compared to singleton births, as well as women with parity >15 (n=40), GA >43 weeks (n=18), and maternal age >53 years (n=7). Thus, 98.6% of women who delivered in medical facilities in Georgia during the study period met the inclusion criteria, for a final analytical sample of 148,407 singleton newborns and their mothers.

On February 1st 2018, Georgia launched a new ANC programme, which is based on the latest WHO recommendations (i.e., eight ANC visits, of which six should be in the third trimester). Therefore, women were considered part of the ‘old’ ANC programme if they had any registered ANC visits before February 1st 2018, or were beyond GA week 12 at February 1st and initiated ANC thereafter. Women were considered part of the ‘new’ ANC programme if they had a registered first visit in the GBR after February 1st 2018 and were below GA week 12 at February 1st. GA week 12 is the threshold at which women should initiate ANC to get financing from the state programme in Georgia.

Exposure

The main exposure was defined as the utilization of antenatal care, as measured by the APNCU index [16]. This index characterizes ANC using two dimensions: GA week at ANC initiation and number of ANC visits, adjusted for GA week at ANC initiation and at GA week at delivery. For each GA week at delivery, the observed number of ANC visits is divided by the expected number of visits at that particular GA week. The APNCU index stratifies ANC into four categories: intensive care, adequate care, intermediate care, and inadequate care. We calculated the expected number of ANC visits according to the APNCU index based on the Georgian guidelines for the old and the new ANC programme separately (Table 1). The observed number of ANC visits was extracted from the GBR for each GA week at delivery. Women who had initiated ANC up to completed GA week 14 and attended 110% or more of recommended ANC visits were categorized as receiving intensive care. Women who had initiated ANC up to completed GA week 14 and attended 80%-109% of recommended ANC visits were classified as receiving adequate care (reference category). Women who had initiated ANC up to completed GA week 14 and attended 50%-79% of recommended ANC visits were categorized as receiving intermediate care, and those who had initiated ANC after completed GA week 14, attended less than 50% of recommended ANC visits, or did not have any ANC visits during pregnancy, were classified as receiving inadequate care.

Table 1. Number of expected antenatal care (ANC) visits for each gestational age (GA) week at delivery.

	Number of ANC visits – Before February 1st 2018 (old ANC programme)			
GA week	Intensive care	Adequate care	Intermediate care	Inadequate care
≥37	≥6	4-5	2-3	0-1
32-36	≥5	3-4	1-2	0
22-31	≥4	2-3	1	0
	Number of ANC visits – After February 1st 2018 (new ANC program)			
GA week	Intensive care	Adequate care	Intermediate care	Inadequate care
≥40	≥9	7-8	4-6	0-3
38-39	≥8	6-7	3-5	0-2
36-37	≥7	5-6	3-4	0-2
34-35	≥6	4-5	2-3	0-1
30-33	≥4	3	2	0-1
26-29	≥4	3	1-2	0
22-25	≥4	2-3	1	0

Outcomes

Study outcomes were NICU admissions and PM. NICU admissions in the GBR were validated using the hospitalization registry, which ensures registration of all patients admitted to hospital, although there is no specific information about NICU admission. Of the 15,072 (10%) newborns with missing information on NICU admission in the GBR, 41 were found in the hospitalization registry during the early neonatal period. Thirty-five of these were categorized as having a NICU admission based on their condition, the urgency of the situation, and the organizational level of the hospital (only level 3 hospitals have a NICU in Georgia). The remaining six cases were classified as not having a NICU admission. In line with internationally accepted definitions, Georgian guidelines define stillbirth as the delivery of a newborn with no sign of life after completed GA week 22 and END as the death of a livebirth during the first 7 days (168 hours) of life. The combination of stillbirth and ENDs is defined as PM. Information on PM cases was validated using VRS data.

Covariates

We drew a directed acyclic graph (DAG) to identify confounding factors. Based on the DAG, we adjusted our analysis for maternal age (≤19, 20-29, 30-39, ≥40 years), parity (nulliparous, multiparous), education (primary, secondary, higher), and region of residence and delivery (resided and delivered in Tbilisi, resided in Tbilisi and delivered outside Tbilisi, resided outside Tbilisi and delivered in Tbilisi, resided and delivered outside Tbilisi). GA was accounted for through the APNCU index.

Statistical analyses

We calculated descriptive statistics for selected maternal characteristics across APNCU index categories. We used logistic regression analysis to assess the associations between APNCU index categories and NICU admission and PM, and conducted sensitivity analyses by running the same regression models stratified by: 1) the old/new ANC programme; and 2) preterm/term newborns. The results are presented as unadjusted odds ratios (ORs) and adjusted ORs (AORs) with 95% confidence intervals (CIs). The chi-square test was used to test whether there was a difference in the proportion of NICU admissions and PM before and after the implementation of the new ANC programme.

The APNCU index only evaluates ANC initiation before completed GA week 14. To enhance our understanding about the importance of timely ANC initiation, women were categorized into three groups: ANC initiation up to completed GA week 12 (reference category), ANC initiation after completed GA week 12 and before GA week 28, and ANC initiation in or after completed GA week 28. We then calculated the odds of PM and NICU admission for women with ANC initiation after completed GA week 12. Completed GA week 12 was used as a cut-off value, as the WHO has identified this as the best period in which to initiate ANC (22). Statistical software STATA (StataCorp, College Station, TX, USA) 16.0 version was used for the analysis.

Ethical consideration

The NCDC Institutional Review Board revised and approved the study protocol (IRB # 2017-010 31.03.2017). The Regional Committee for Medical and Health Research Ethics, North Norway, approved the use of the data from the GBR for research purposes (2017/404/REK Nord).

Results

In total, 5.3% of our study women did not have any ANC visits registered in the GBR. According to the APNCU index, 16% of women received inadequate care, 10% intermediate care, 38% adequate care, and 36% intensive care. From 2017 to 2019, the proportion of women who received adequate care decreased, whereas the proportion receiving intermediate care increased slightly (Fig. 1).

Mothers below 19 years of age had the highest proportion of inadequate care (23%) compared to mothers in other age groups. Seventeen percent of multiparous women and 26% of women with primary education received inadequate care, which was higher than the proportion of primiparous women with higher education. Women in the age group 30-39 years (38%) who gave birth to their first baby (41%) and had higher education (44%), had a higher proportion of intensive care than the other age groups, multiparous women, and women with primary education. Also, 42% of those who lived and delivered in Tbilisi received intensive care (Table 2).

Table 2. Maternal characteristics by Adequacy of Prenatal Care Utilization index categories presented as frequencies and row percentages.

	Intensive (n=53,794), 36%		**Adequate** (n=56,841), 38%		**Intermediate** (n=14,800), 10%		**Inadequate** (n=22,972), 16%	
Maternal age, years								
≤19	1047	28	1375	37	443	12	874	23
20-29	31,165	36	34,026	39	8814	10	12,948	15
30-39	19,693	38	19,547	37	5070	10	8109	16
≥40	1889	36	1893	36	473	10	1041	20
Parity								
Nulliparous	23,693	41	21,138	37	5182	9	7194	13
Multiparous	30,047	33	35,663	39	9608	11	15,756	17
Education								
Primary	2640	21	5143	42	1402	11	3135	26
Secondary	21,830	33	28,167	42	6548	10	10,370	16
Higher	23,280	44	19,169	36	5328	10	5453	10
Unknown	6044	38	4362	27	1522	10	4014	25
Region of residence/delivery								
Lived and delivered in Tbilisi	20,507	42	16,234	33	5397	11	7241	15
Lived in Tbilisi, delivered outside Tbilisi	440	34	467	36	185	14	195	15
Lived outside Tbilisi, delivered in Tbilisi	7721	36	7541	35	2558	12	3546	17
Lived and delivered outside Tbilisi	25,125	33	32,594	43	6655	9	11,878	16
Preterm birth	4500	8.4	3642	6.4	678	4.6	1995	8.7

Among the 148,407 singleton newborns, the NICU admission rate was 7.8% (95% CI 7.7-7.9); there were 1717 PM cases, 431 ENDs, and 1286 stillbirths. During the study period (2017-2019), the overall PM rate among singletons was 11.6 (95% CI 11.0-12.1) per 1000 births; END and stillbirth rates were 2.9 (95% CI 2.7-3.2) per 1000 livebirths and 8.7 (95% CI 8.2-9.1) per 1000 births, respectively. Women who received intermediate care had the lowest rates of NICU admission (7.0%), preterm birth (4.8%), PM (6.9 per 1000 births), ENDs (2.1 per 1000 livebirths), and stillbirth (4.8 per 1000 births). Rates of NICU admission (8.8%) and preterm birth (8.6%), as well as PM (16.9 per 1000 births), END (3.9 per 1000 livebirths), and stillbirth (13.1 per 1000 births) rates were higher among women who received inadequate care compared to the other groups (Tables 2 and 3).

Table 3. Neonatal intensive care unit (NICU) admission rates, perinatal mortality (PM), early neonatal death (END), and stillbirth (SB) by Adequacy of Prenatal Care Utilization index categories among singleton newborns.

	Intensive (n=53,794), 36%	**Adequate** (n=56,841), 38%	**Intermediate** (n=14,800), 10%	**Inadequate** (n=22,972), 16%
NICU (%)	4469 (8.3)	4066 (7.2)	1035 (7.0)	2019 (8.8)
PM, n *(per 1000 births)*	561 (10.4)	665 (11.7)	102 (6.9)	389 (16.9)
ENDs, n *(per 1000 livebirths)*	161 (3.0)	151 (2.7)	31 (2.1)	88 (3.9)
SB, n *(per 1000 births)*	400 (7.4)	514 (9.0)	71 (4.8)	301 (13.1)

There were 82,330 mothers and singleton newborns in the old ANC programme, and 66,077 in the new ANC programme. The proportion of NICU admissions in the old and new ANC programmes was 6.8% (95% CI 6.6-7.0) and 9.1% (95% CI 8.8-9.3), respectively (p<0.01).

The number of PM cases was 911 (261 ENDs and 650 stillbirths) and 806 (170 ENDs and 636 stillbirths), respectively. The proportion of PM in the old ANC programme was 11.1 per 1000 births (95% CI 10.4-11.8), compared to 12.2 per 1000 births (95% CI 11.4-13.1) in the new program (the difference between proportions was statistically significant *p*=0.04).

Women who received inadequate care had 16% (AOR=1.16, 95% CI 1.09-1.23) increased odds of delivering a newborn who was admitted to NICU and 18% increased odds of experiencing PM (AOR=1.18, 95% CI 1.02-1.36) compared to women who received adequate care. Newborn whose mothers received intensive care had 16% increased odds of being admitted to NICU (AOR=1.16, 95% CI 1.11-1.22) compared to newborns whose mothers received adequate care. The odds of experiencing PM among women who received intermediate care was 44% lower (AOR=0.56, 95% CI 0.45-0.70) than for those who received adequate care (Table 4). The results we observed for the associations between APNCU index categories and NICU admission or PM in the regression models stratified by old/new ANC programme and preterm/term newborns were mainly in agreement with the results for the total study sample; women receiving inadequate care had higher odds of NICU admission (both programmes) and PM (old programme). Newborns of women receiving intensive care experienced higher odds of NICU admission (both programmes) and those with mothers receiving intermediate care had significantly lower odds of NICU admission (new programme) and PM (both programmes) compared to the adequate care group (Table 5). Term newborns of women in all APNCU index categories had increased odds of NICU admission when compared to term newborns of women receiving adequate care, while the odds of the same outcome were not statistically significant for preterm newborns. The odds of PM were lower among women receiving intensive care compared to those receiving adequate care for both term and preterm newborns; similar odds were observed for intermediate care, but only for preterm newborns. The highest odds of PM were found among term newborns whose mothers received inadequate care (Table 6).

Table 4. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CIs) for the associations between Adequacy of Prenatal Care Utilization index categories and neonatal intensive care unit (NICU) admission and perinatal mortality (PM) among singleton newborns.

Exposure	**NICU admission**			**PM**		
APNCU index category	n cases	OR (95% CI)	AOR (95% CI)	n cases	OR (95% CI)	AOR (95% CI)
Intensive	3887	1.18 (1.12-1.23)	1.16 (1.11-1.22)	501	0.89 (0.80-0.99)	0.91 (0.81-1.03)
Adequate	3735	1.0	1.0	618	1.0	1.0
Intermediate	936	0.98 (0.91-1.05)	0.97 (0.90-1.05)	92	0.59 (0.48-0.72)	0.56 (0.45-0.70)
Inadequate	1587	1.25 (1.18-1.32)	1.16 (1.09-1.23)	284	1.45 (1.28-1.65)	1.18 (1.02-1.36)

The models are adjusted for maternal age, parity, education, region of residency and delivery.

Table 5. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) for the associations between Adequacy of Prenatal Care Utilization index categories and neonatal intensive care unit (NICU) admission and perinatal mortality among singleton newborns for women eligible for the old and new antenatal care (ANC) programmes, separately.

	Old ANC programme	**New ANC programme**
NICU admission	AOR (95% CI)	AOR (95% CI)
Intensive	1.17 (1.09-1.25)	1.14 (1.07-1.22)
Adequate *(reference)*	1.0	1.0
Intermediate	1.07 (0.95-1.20)	0.82 (0.74-0.90)
Inadequate	1.14 (1.04-1.25)	1.10 (1.01-1.20)
Perinatal mortality		
Intensive	0.90 (0.77-1.06)	0.91 (0.76-1.09)
Adequate *(reference)*	1.0	1.0
Intermediate	0.63 (0.45-0.88)	0.48 (0.36-0.65)
Inadequate	1.27 (1.04-1.54)	1.06 (0.86-1.31)

The models are adjusted for maternal age, parity, education, region of residency and delivery.

Table 6. Adjusted odds ratios (AOR) and 95% confidence intervals (CIs) for the associations between Adequacy of Prenatal Care Utilization index categories and neonatal intensive care unit (NICU) admission and perinatal mortality among preterm and term singleton newborns.

	Preterm (GA week 23-36)	**Term (GA week 37-43)**
NICU admission	AOR (95% CI)	AOR (95% CI)
Intensive	1.00 (0.91-1.10)	1.08 (1.01-1.15)
Adequate *(reference)*	1.0	1.0
Intermediate	1.09 (0.91-1.29)	1.14 (1.04-1.25)
Inadequate	1.06 (0.93-1.20)	1.14 (1.05-1.23)
Perinatal mortality		
Intensive	0.72 (0.63-0.84)	0.76 (0.59-0.97)
Adequate *(reference)*	1.0	1.0
Intermediate	0.67 (0.50-0.89)	0.82 (0.57-1.19)
Inadequate	0.98 (0.82-1.17)	1.37 (1.05-1.79)

GA: gestational age

The models are adjusted for maternal age, parity, education, region of residence and delivery.

The associations between GA at ANC initiation and NICU admission and PM were not statistically significant, except for late ANC initiation (at GA week 13-28), which increased the odds of NICU admission by 14% (AOR=1.14, 95% CI 1.06-1.23) compared to those with early ANC initiation (before GA week 12).

Discussion

In this study of singleton pregnancies from Georgia in 2017-2019, we found that the majority of pregnant women did not receive adequate ANC (62%) and that the utilization of ANC was significantly associated with NICU admission and PM. The lowest PM rate was found among women who received intermediate care, and the highest rate among women with inadequate care. Specifically, our results indicate that inadequate care (no ANC, less than 50% of recommended ANC visits, or ANC initiation after the first trimester) increased the odds of newborn admission to NICU by 16% and the odds of PM by 18%. These findings are in line with other studies [1, 5, 6, 26]. Another important finding was that women who received intensive (36%) and inadequate care (16%) were overrepresented in our study sample, representing higher proportions than in other countries [6, 21, 27, 28].

Previous studies have suggested a U-shaped relationship between ANC utilization and PM. Women with both inadequate care and extra ANC visits have shown higher risks of poorer birth outcomes [29-31], as extra ANC visits are determined by morbidity during pregnancy. In our study, women receiving intermediate care had 44% decreased odds of experiencing PM compared to those receiving adequate care. Women who received intensive care did not experience higher odds of PM than those receiving adequate care. On the other hand, they experienced 16% increased odds of newborn admission to NICU, which may indicate a higher proportion of morbidity in these pregnancies, although no increase in PM rate. There are several possible explanations for this finding. Theoretically, women who receive intensive care are more likely to have a high-risk pregnancy, and they could have benefited from these extra ANC visits and from NICU admission. However, the number of women receiving intensive care was larger in Georgia compared to other countries, which may suggest an overuse of medical services in this subset of pregnant women. The high proportion of women attending more than recommended number of ANC visits could be an effect of some healthy women, especially older, nulliparous women with higher education, attending self-initiated extra ANC visits that are not necessary from a medical point of view. Further, the fact that women who received intermediate care experienced the lowest odds of PM and NICU admission, may suggest that: 1) those with low-risk pregnancies do not necessarily have to complete all recommended ANC visits, as the intermediate care group seems to include women with the healthiest, morbidity-free pregnancies; and 2) that well-performed screening during ANC properly identifies high-risk pregnancies. This suggests that the number of ANC visits should be determined on an individual basis for each women, based on risk assessment. These suggestions are supported by previous research, which has shown that goal-oriented, effective ANC with four or five visits does not affect perinatal outcomes when compared to eight ANC visits, but is more cost-effective [32]. Furthermore, over-medicalization of childbirth has become common practice in many settings, which can include unnecessary, or even inappropriate interventions [33]. Limited access to data about maternal complications did not allow us to investigate the reasons for extra ANC visits, and although the proportion of women who received intensive care was higher than expected, we cannot confirm our hypothesis about unnecessary ANC visits among a subgroup of women receiving intensive care.

In line with other studies, we observed increased odds of NICU admission and PM in women receiving inadequate care [27, 34]. The odds of NICU admission for the inadequate care group, i.e., women who initiated ANC after GA week 14 or attended <50% of recommended ANC visits, increased by 16% compared to the adequate care group. Similar to our findings, previous research reported statistically significant, increased odds of NICU admission for extremely preterm newborns without active antenatal management [34], severe perinatal morbidity for all newborns [30], as well as increased risk of stillbirth and ENDs [6] and preterm birth [21, 31]for women in the inadequate care group, compared to the adequate care group.

The majority of pregnant women in Georgia who delivered singleton newborns during the study period started their ANC before GA week 12 (85%). The timing of ANC did not seem to have a substantial impact on NICU admission or PM, except among women who initiated ANC at 13-28 GA weeks, who experienced higher odds of their newborns being admitted to

NICU. A similar finding was provided by a study from Cape Town, which suggested that ANC initiation was not a determinant of stillbirth [35].

Another important finding of our study was that there was no decline in the proportion of NICU admissions or PM after the implementation of the new ANC programme, which supports the idea that the number of ANC visits itself does not have an impact on the outcome, but the risk assessment during ANC, and thus, quality of care, is much more important. In fact, there was a significant increase in both NICU admissions and PM and after the implementation of the new ANC programme. Nevertheless, our rather short study period may not be long enough to draw valid conclusions. Also, the effectiveness of the new ANC programme cannot be evaluated only by the proportions or ORs for different time points; therefore more research that takes into account morbidity data is needed. However, our findings indicate that the new ANC programme does not reduce NICU admissions or PM in Georgia. Thus, it might be that the number of ANC increased with the new ANC programme, but the quality and amount of ANC provided remained the same.

Furthermore, stratified analyses by pretem/term birth showed that NICU admission was significantly associated with intensive, intermediate, and inadequate care among newborns born after completed GA week 37. Interestingly, the odds of PM were lower for term and preterm newborn in the intensive care group. These findings strengthen the above-mentioned explanations – women receiving intensive care benefited from extra ANC visits; however, this group might include women with self-initiated unnecessary visits. Additionally, this analysis showed that the impact of ANC utilization on NICU admission and PM, especially for inadequate care, is larger among women who delivered after completed GA week 37, and this finding is in line with previously reported results [36, 37].

Only a few studies have assessed the association between ANC utilization and NICU admission/PM, and this study represents the first attempt to address this issue in the Georgian population. The main strength of the study was that we included all women who delivered a singleton baby in Georgia during a 3-year period. The main outcome was validated by the VRS, and the agreement between the GBR and the VRS was high (99.8%). Additionally, we used the most recent and valid index for ANC utilization, and the number of ANC visits was calculated based on current practice and guidelines in Georgia.

The main concern in studies that assess the relationship between ANC and pregnancy outcomes is the definition of adequacy of care. Crudely, number of ANC visits, even after adjustment for GA and ANC initiation, does not precisely assess the impact of ANC on the outcomes [38]. No indices that exist for assessing ANC utilization take into account the quality of care provided during ANC visits. Therefore, neither the quality of provided care, nor the risk conditions of woman is considered in the results derived from this index, which can be seen as a limitation of this study. The APNCU index has also been criticized for introducing bias, since women shorter pregnancies and frequent ANC visits are more likely to be included in the intensive care group, which complicates the possibility of studying the impact of a ANC on preterm birth or low-birth weight newborns [39]. However, all indices have arbitrary thresholds, which always leads to slight, possible misclassifications between groups, although it does not lead to substantial bias for associations between index groups and outcomes [29]. Additionally, we did not analyse high-risk women separately, and the final analyses were not adjusted for maternal diseases during pregnancy, as complete information about maternal diseases during pregnancy is not yet available in the GBR. However, we assume that the results would only be slightly different if we could adjust for maternal diseases, as GA at delivery and maternal diseases are strongly correlated, and length of gestation is considered in the APNCU index itself. Additionally, other studies did not adjust for maternal diseases, and those who did, did not observe substantially different results after controlling for maternal diseases [6, 40].

Despite the limitations, the present results provide support for the conceptual premise that increasing the number of ANC visits does not have a significant impact on reducing NICU admissions or PM rates in a country like Georgia. All women should be offered the minimum set of ANC regardless of their risk level, and women who need additional care should be identified. As has been shown in other countries, separate definitions of routine recommended care should be created for high- and low-risk pregnancies, and additional ANC visits should be scheduled based on individual women's needs [41, 42]. Inadequate care, as well as unnecessary overutilization of ANC, can lead to harmful outcomes for women and newborns. Our study results highlight the importance of studying maternal knowledge in reproductive health as well as investigating the quality of ANC.

Conclusion:

Women receiving inadequate care had the highest odds of NICU admission and PM, whereas women with intermediate care during pregnancy experienced the lowest odds. Sixty-two percent of pregnant women who delivered in Georgia during 2017-19 did not receive adequate care. Increasing the number of ANC visits does not seem to be effective for improving NICU admission or PM rates.

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