Multi-Causal Phenomenon of Preterm Delivery (Epidemiological Review)

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Summary

Major reasons for infant morbidity around the world are preterm delivery, infections, and complications. Premature children, who succeed to live, often have health-related issues. Medicine today uses modern achievements in diagnostics to reveal potential preterm delivery. Possible syndromes of preterm delivery are of heterogeneous nature, and include biological, social, and psychological factors. It's a sad fact, but even "healthy" mothers give birth to premature babies. Various surveys described in this article are clear proof of that. Together with clinical issues of preterm delivery, medical-technical issues should also be considered alongside with ethical norms and legal issues of obligation of treatment or refusal to treatment. Psychological side is also of importance, since birth of a premature baby usually poses stress to the family, where adults require moral support to resolve it in a dignified manner. To reduce the burden of health complications resulting from preterm delivery, it is necessary to find ways for completing the full term of pregnancy, at least until week 39. For this, the quality of care for pregnant women and infants should increase, new preventive and treatment measures are to be found, and new global initiatives need to appear.

Abbreviations: WHO – World Health Organization; OR – Odds Ratio; RR – Relative Risk 95%; CI – 95% Confidence Interval; BMI – Body Mass Index; JOG – British Journal of Gynecology; NCDC – National Centre of Disease Control;

***Key words*:** preterm delivery, risk factors, epidemiology

Introduction

There is no doubt that various pathologies of intranatal and postnatal period may reflect on etymology and pathogens of many diseases during adulthood. Preterm delivery, along with related medical complications, is one of such pathological conditions. Premature infants fall under the high-risk group for developing cerebral palsy and mental development issues. All premature children have high risk for developing minimal brain dysfunction, including speech and vision impairment, lack of concentration, and difficulties in learning. There is also a high risk for neurological-psychical development heavy delays. Some authors also describe heavy delay of cognitive as well as motoric skills on late stage of ontogenesis (ITV. 2011).

- ◊ There are 15 million deaths of premature infants in the world
- ◊ 1.1 million premature newborns cannot be saved
- ◊ Prevalence of preterm delivery in different countries is 5-18%
- ◊ 80% of premature babies are born at the week of 32-37, and majority survive thanks to the modern infant care standards.
- ◊ Prevention of over 75% of premature births is possible without intensive medical intervention.
- ◊ Brazil, USA, India, Nigeria have some of the highest rates of preterm delivery, indicating global scope of the problem.
- ◊ Poor countries have 12% of preterm delivery, as opposed to 9% in high income countries. Poor families usually have higher risks (World Health Organization 2012).

Data from 190 countries, as assessed by WHO, indicates preterm delivery as the cause of 36% of infant deaths in 2012 (Lawn, JE. 2014).

Even though doctors have high success with child health, small birth weight, prevention of preterm delivery and its forecast is still a challenge. In spite of decades of work, scientists could not come up with effective means for preventing preterm delivery. Introduction of cost-effective treatment and prevention measures is a challenge for the modern society (Helmer, H. 2007). WHO guidelines indicate need for creation of the effective services by healthcare organizations, and giving medical personnel relevant information on effective treatment of pregnant women and premature babies (WHO report 2015).

In a long run, premature birth is associated with the quality of life, and need for intensive use of medical services, which, in turn, result into high costs of the healthcare services used by the individual. Some countries have counted the cost, which, for example, totals up to €50,800 for Germany, whereas standard medical service for the timely born infants for a tear is only €5,800 during the first year of life. (Kirschner, W. 2007; March of Dimes, 2009). Each year, Germany spends about €3.3 billion on medical services of the premature babies. Increase of costs is usually associated with intensive use of stationary service. Compared to timely born babies, infants with less than 37 weeks of gestation period use medical services three times more intensively, while the intensiveness of use of medical services by those born under 32 weeks is 7 times higher (Kirschner, W. & Mylonas, 2014).

In 2005, USA spent about $2.2 billion out of healthcare budget on preterm delivery. Hospitalization of 24+0 _24+6 premature infants cost $203,000 per infant (Winckel, UC. 2010).

However, apart from hospitalization, there are numerous other factors that are associated with preterm delivery:

- ◊ Costs of delivery
- ◊ Early integration cost
- ◊ Development-related education cost
- ◊ Disability-related rehabilitation cost
- ◊ Lifetime care cost
- ◊ Financial support from the family
- ◊ Lack of productivity resulting from development issues.

Costs associated with prematurity are directly proportional to the delivery term, and is especially large for extremely young premature infants.

Longitude study conducted by English and Irish scientists show that length of use of stationery services by premature children during first 10 years of life is twice longer than for those born at the right term (Petrou S. BJOG, 112 Suppl 1:10-5).

These figures show the importance of proper prevention and management of preterm delivery for a country with healthcare system like in Georgia (under the conditions of low income population and expensive medical care).

- ◊ According to WHO data, in 2013, about 1,1 million cases of child deaths out of 6,3 million resulted from complications caused by preterm delivery.

- ◊ In 2014 over 200 countries participated in activities and over 60 countries planned special activities to raise awareness of the population on health of premature children, infants and mothers.

- ◊ In 2015 complications resulting from preterm delivery have not lost its importance, and remained cause for majority of child deaths.

Similar to other counties in transition, Georgia has its healthcare-related problems, including those in reproductive medicine. There is a need for finding effective solutions to these problems. Preterm delivery is one of them. According to official statistics, Georgia has maintained its 9.7% indicator for preterm delivery during 2014-2015 (NCDC). However, the same source indicates 6.7% as the rate for premature infants (Table 1).

National Center for Disease Control and Public Healthcare
Weight of live- and still-born babies at the time of birth (maternity house data)
Georgia, 2014

	Total					
Live births	30235	161	401	3085	51666	4922
% of total live births	100.0	0.3	0.7	5.1	85.8	8.2
Stillborn	637	264	95	129	132	17
% of total stillborn	100.0	41.4	14.9	20.3	20.7	2.7

Source: National Center for Disease Control and Public Health

Regardless of decreasing tendency of neonatal and perinatal mortality in Georgia, introducing and applying experience of countries that have accumulated significant experience in newborn treatment and nutrition, and adapting to Georgian context, is of huge importance. Medical issues of premature newborns (incubation, nutrition, morbidity, mortality) require in depth medical study, their medical rehabilitation, adaptation, and integration into the environment.

Georgia still has no statistics available on the improvements of care for premature infant survival, or opportunities for their full mental and physical development. Lack of statistics is the reason why current prevention, treatment and management guidelines were created based on non-Georgian data.

Definition

Medical literature defines preterm delivery as childbirth that takes place within the interval of less than 260 days from the last menstrual period (37 weeks). WHO considers infants under 2,500 grams of weight as premature. Weight indicators are based on epidemiological studies, according to which babies that weigh less than 2,500 grams have 20 times higher rates of mortality. Weight criteria was developed during 1948 Assembly meeting. Later, prematurity was defined as that of less than 38 weeks of pregnancy (Helmer, H. 2007).

Small body weight of infants may serve as the reason for growth and developmental delays. However, another studies found that often there is varying correlation between infant body mass and pregnancy term. It was decided to create a classification that would be focused on the growth and development of the infant, and following categories were adopted: infants that are "small for pregnancy term," "corresponding to pregnancy term," and "big for pregnancy term."

International statistical classifier, ICD-10 covers length of pregnancy as well as body mass of the newborn:

P07.0 newborns with very little body mass (<999 grams)
P07.1 newborns with little body mass (1000–2499 grams)
P07.2 very premature newborns (pregnancy term <28 weeks/<196 days)
P07.3 premature newborns (28–36 weeks/<256 days)

Prematurity classification is different across countries. Many leading European countries standardizes reproduction data based on pregnancy term, since research of the first trimester standard helps determining exact pregnancy term with ±3 day precision (Klimont, J.2012).

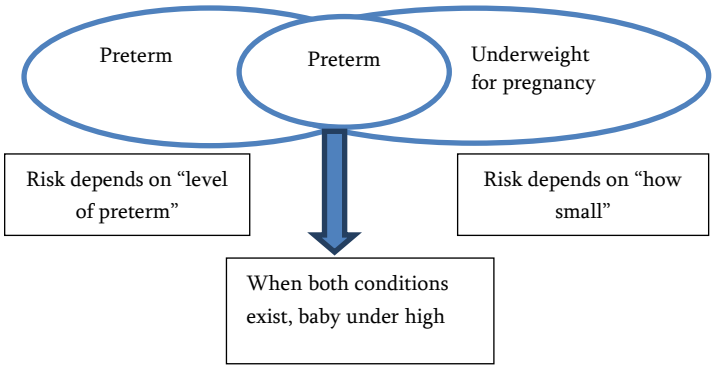
It is important to know what are the criteria used by the country to determine prematurity, since it defines the condition of the given country in relation to this phenomenon. For example, Austria, based on one of the criteria, used to have the highest preterm delivery rates, but change of criteria showed different statistics of this country (Helmer, H. 2007).

Clinical, evidence-based actions, including research of the lung function of the infant, tokolysis, antenatal transportation, transfer to neonatal intensive care unit is done depending on the pregnancy term. As a result, newborns are classified based on the pregnancy term (Helmer, H. 2007). The most desirable "Gold Standard" for determining pregnancy term is early ultrasound of fetus development parameters during the first trimester. Determining pregnancy term based on the menstrual cycle remains as the only standard in many countries. However, countries also use combined method of ultrasound results and latest menstrual cycle to determine the term. This algorithm is especially important in terms of reporting prematurity.

Different categories of "Small baby"

"Small baby"

Picture 1



"Small Baby" is a heterogenic group of the embryo: prematurely born with sufficient weight, timely born with low body mass compared to pregnancy term (picture 1), prematurely born with small body mass. Not all prematurely born babies are "small" and vice-versa (WHO report 2012).

According to WHO recommendation newborns or embryos with weight above 500 grams should be statistically registered.

Newborns with less than 2,500 grams of body mass are distributed into the following groups:

◊ Small body mass of the newborn: less than 2,500 grams
◊ Very little body mass: less than 2,500 grams
◊ Extremely small weight: less than 2,500 grams (Klimont, J., 2007)

Classification below is based on the data of infant morbidity and mortality.

Classification of prematurity based on pregnancy term:

Table 2

Pregnancy term (completed pregnancy week)	Name
<24+0	Extreme prematurity
from 24+0 to 27+6	Very early prematurity
from 28+0 to 33+6	Early prematurity
from 34+0 to 36+6	Moderate prematurity

Scientific literature offers recommendation, according to which lower threshold should start from the gestation age, from 22+0 weeks (Helmer, H. 2014).

Prematurity from 34+0 to 36+6 is referred to as "marginal," "average" in the literature. For this group, in 1992-2002 14% increase of incidence is in place, and these newborns are characterized with high morbidity and mortality compared to regular newborns. It was expected that this group was to be as safe as regular newborns, but unfortunately, epidemiological research proves otherwise (Helmer, H.2007).

Moderate premature newborns are 80% of the total number, while their share has increased by 15-40%, most frequently to 36+0_36+6 weeks of pregnancy. The picture changes in case of one or more variables. According to Swiss data (2008), moderate premature birth is caused by:

- ◊ 30-45% spontaneous caesuras of the uterus
- ◊ 30-35% early disorder of uterus deciduas
- ◊ 30% gynecological, or reasons of mother, or embryo (medical issues)
- ◊ 6% unknown reasons.

According to the research undertaken, it is possible to prevent later prematurity (Holland, M.G. et al., 2009).

According to the Georgian guidelines on prevention of preterm delivery and its management, preterm delivery is a child birth from week 22 0/7 to week 36 6/7. According to the same guideline, based on gestation term there are two categories of childbirth:

1. Preterm delivery at early term of gestation (22 0/7 - 33 6/7 weeks)
2. Preterm delivery at later term of gestation (34 0/7 - 36 6/7 weeks)

Risk-factors of pre-term delivery – review of epidemiological research

There are various epidemiological studies conducted internationally on preterm delivery, but the intensiveness of researching this issue is very low compared to others. Therefore, defining risk-factors is also under a question. Scientific research on preterm delivery is followed by heterogeneous results. The reason for different countries could be:

Strictly different social and public characteristics
Formats of provision of various medical-gynecological services
Pregnancy management under the conditions of various healthcare and regulation systems
Various risk groups
Various intervention opportunities.

Study of prematurity pathogenesis and mechanism requires revision of epidemiological data. Various factors that are associated with components of a mother, father, and embryo separately, or in combination, are linked to this phenomenon.

Preterm delivery epidemiology is focused on identification of risk-factors, finding information and experience on how to intervene on an early stage to optimize prematurity.

However, there are many components listed in the literature that seem to be of multi-causal nature. Often the risk is associated with physical and spiritual comfort of a pregnant woman. Social and economic situation of a pregnant woman, workload and stress situation in combination can be vital for the health of the mother as well as the baby.

Risk-factors often remain unknown in case of spontaneous preterm delivery. Some of the known risk-factors are complex, and are not studied well yet.

Based on selective review of PubMedi literature using keywords "preterm delivery," "preterm birth," "tocolisis", 1996-2002 relevant randomized research conclusions, systematic resumes and meta-analysis, European, British and US scientific unions have named various separate and combined factors for premature birth. (Murphy, D J. 2012).

Infections

Connection of infections with premature birth is supported by the following assumption: bacterial infections reach into uterus and amniotic fluids, result into inflammation and early compressions of the uterus or rupture of the embryo membrane. According to Goldenberg et al. (2000), about 80% of pregnant women until the term of 30 weeks and 30% of those until the term 37 weeks have tested to have bacterial infections in amniotic fluids.

infections in amniotic fluids.

Chronic stress

According to empirical data of prospect survey of the population, in cases of social and spiritual tension caused to pregnant mothers as a result of stressful situations, newborns are either significantly underweight, or are born before 37 weeks, since stimulation of hypothalamus-hypophisis-kidney gland stimulates childbirth process.

Studies show that corticotrophin hormone in placenta is linked to spontaneous early delivery. According to Scandinavian body of research, stressful life situations and preterm delivery are in direct connection with each other (Austin, MP & Leader L 2000).

Heavy reproduction anamnesis

Probability of preterm delivery in case of previous preterm delivery is 20%, and 40% in case of two previous cases (Winckel, U.C 2010).

A study of 150,000 deliveries conducted in the US showed that previous record of spontaneous preterm delivery with one baby creates a high risk during the next delivery (OR 3.6 ; 95% CI 3.2-4.0). Same correlation was identified for women that had iatrogenic preterm delivery (OR 1.6 ; 95% CI 1.3-2.1). These pregnant women have the biggest risk during the same gestation period of future pregnancies (Anath ,C.V. 2006).

Multiple gravid (about 10% of all premature born babies)

According to Swedish population registry, coefficient of preterm deliveries are reduced in case of one baby, but are increased in case of more than one gravid (Morken NH, 2005).

Surveys in Taiwan show that women with less than 12 month interval between pregnancies are more prone towards preterm delivery (OR 4.2; 95% CI 3.0-6.0) (Slieh TT, 2005). The risk decreases when interval between pregnancies increases to 18-49 months (Krymko H, 2004).

Inconvenient socio-economic conditions.

According to studies in Scotland, 1980-2000 analysis, increase of preterm delivery risks(risk change OR from 1.52 to 95% in 80-ies CI 1.44-1.61 OR 1.75 ; 95% CI to 1.65-1.86 towards the end of 90-ies) was associated with worsened social situations (Fairley, K. 2006). European body of research cannot determine correlation between working mothers and preterm delivery, but unhappiness with the workplace is significantly related with preterm delivery.

Pregnancy below the age of 18 and above 35

Age of the mother is an important factor for health of the baby. This concerns premature births as well (SOEPpaperson Multidisciplinary Panel Data Research, 2010).

There are different data concerning the young age of the mother and preterm delivery. Study from Brazil showed high prevalence of teenage pregnancies (29%), when comparing pregnant women of under 18, 18-19, and 25-29 years of age. Risk of preterm delivery was high amongst pregnant women under 18 (OR 1.7; 95% CI 1.02-3.08), but the risk was no higher than that of 18-19-year-olds. This could indicate that the link between young mothers and preterm delivery could be resulting from genetic factors (Eure ,CR.; Lindsay, MK. & Graves, WL. 2002).

Weight of the pregnant woman

BodyCare research (Germany) shows that weight of a pregnant woman, social status, and alcohol consumption are in direct correlation and pose double effect on preterm delivery. The survey shows that 3.1% of pregnant women with problematic level of alcohol consumption is mainly of low social status, and overweight (Dudenhausen, J. W.; Kirschner, R. 2011).

Systemic analysis of epidemiologic surveys show that extreme weight of the mother during pregnancy and preterm delivery are connected to each other through three anthropological lines: BMI, weight increase of a pregnant mother, and height of a mother. This study showed exact linkages between these factors. Main criticism came from formulation of outcome for pregnancy before 37 weeks, and recommendations were made to define 32-34 weeks for pregnancy outcomes.

Other studies assessed combined effect of BMI before pregnancy and weight gain during pregnancy for two categories of preterm delivery – 20-21 weeks and 32-36 weeks (Dietz, PM.; Callaghan, WM., 2006). Correlation between little weight gain and very small premature babies was established, which was especially obvious for very thin women (adjusted OR 9.8, 95% CI 7.0-13.8). Mothers with significant weight gain during pregnancy showed twice as many odds together with giving birth to premature children.

Physical activity before pregnancy, regardless of BMI is correlated with weight and weight gain, but it should be differentiated according to physical activity.

Study of low income women of the US showed that free activeness during ≥60 days of the first and second trimester is a protective factor of preterm delivery (less than 37 weeks of pregnancy) (OR 0.51, 95% CI 0.27-0.95). However, the risk of preterm delivery increases if pregnant women have to use stairs more than 10 times a day (OR 1.60, 95% CI 1.05-2.46) (Misra, DP.1998).

Sex of the premature newborn

Norwegian studies show that male premature babies are significantly more prone to death in their childhood than females; both of them lack of reproductive skills, and females are prone to bearing premature babies themselves.

More boys are born prematurely. Number of male premature babies is 14% higher compared to females. Premature boys are also more prone to cerebral disorders and have less academic achievements than girls. Scientists explain this with the reason that in case of male embryo mothers suffer more placental issues, and therefore, infections and eclampsia is more intensive. Female embryo develops faster, and its lugs are better developed (Swissmom Newsticker, 4.10.15).

Nutrition during pregnancy

Chinese research suggests that women that take multivitamins before pregnancy, have less risk of preterm delivery (OR 1.59, 95% CI 0.12-2.76 and OR 0.40, 95% CI 0.12-1.40).

In western population, the importance of Omega 3 as a secondary prevention for increasing the length of pregnancy was proven by studies (Facchinetti, F.; Fazzio, M. & Venturini, P. 2005).

Consumption of coffee during pregnancy

This factor was investigated by Italian study of 2000 pregnant women through case-control mechanism, which showed that low dosage of coffee is not linked to preterm delivery (Chiaffarino, F.; Parazzini, F.; Chatenoud, L. et al; 2006).

Unhealthy lifestyle

There is a lack of information on life conditions and lifestyle of pregnant women (Kirschner, K. 2013). Older gravidas with modern lifestyle, attitudes towards starting a family, lowering support to already existing families, breaking relationship stereotypes, especially in large cities, social inequality factor, psychological attitude of women during pregnancy – all of these factors reflect on preterm delivery.

Lifestyle is determined by following criteria: personal decisions, external factors, socio-cultural and economic factors.

Lifestyle can be of two types, as it applies to reproductive function:

1. Those that start families in early ages are less informed on family planning and often end up with large families under inconvenient social conditions
2. Those that first plan career, social stability, and then start family and have children.

Both types of families have both advantages and risks.

Criteria for healthy lifestyle are: average weight, food filled with vitamins and minerals, spiritual stability, good sleep, participation in healthcare prevention programs, leading life free of alcohol, nicotine, and drugs, stable family structure, social support, active rest (sport, music). Lifestyle, which negatively reflects on the health of a pregnant woman is: stress and social tension, tendency towards psycho-pathological, immunology factors for infectious diseases. Study in the US shows that during the period of 2001-2009 number of women leading healthy lifestyle increased from 7.3% to 21.2% (Goeckenjan, M. 2012).

Picture 2

Studies allow to conclude that population of pregnant women experience nutrition issues. This is especially true about supply of iodine, folic acid and iron. Lack of such microelements is linked with preterm delivery alongside with other diseases (Friese, K. Dudenhausen, 2003). Partially, it also results from lack of awareness.

Conclusion

There are many clues to the aetiologies of preterm labour within carefully conducted epidemiological and environmental studies. It is clear that no single approach will be effective for prevention or treatment as there appear to be complex interactions between maternal anthropometry, environmental exposures and genetic susceptibility of the mother and fetus. A careful antenatal booking history can screen for risk factors for preterm delivery, although the predictive value and specificity of scoring systems are poor.

A combined approach to research encompassing epidemiology, pathophysiology and clinical care is required to understand the aetiologies, prevention and optimal management of preterm delivery.

A coordinated research approach that brings together the disciplines of epidemiology, laboratory based science and clinical trials offers the best hope of significant advances in this important aspect of perinatal care.

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