

Incidence of common complications of pregnancy in a municipality in North-West Russia

-A study from population-based birth registry

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Preface

This master program was carried out from August, 2011 to June, 2012 at the Department of Animal and Aquacultures Sciences and Department of Plant and Environmental Sciences, Norwegian University of Life Sciences, in ÅS, a beautiful town near by Oslo, Norway.

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Abstract

Objectives: This is a population-based birth study based on the data from Monchegorsk, which is a town in the central part of Murmansk Oblast in North-West Russia. The main objectives are to determine the incidence of common complications in Monchegorsk during 1973-2005, estimate the relevant risk factors to the complications, the relationship between complications, and analyze outcomes of the newborns.

Method: The data were obtained from the Kola Birth Register from 1973 to 2005. International Classification of Disease, 10th Revision, codes were used to record the complications. Incidence of the selected complications of pregnancy was described. Annual numbers of selected complications were divided into 5-year groups. The incidence in different time periods at 2001-2005 and 1976-1980 was compared by using odds ratio. Chi-Square test for independence and odds ratio has been conducted to indicate the association between the most frequent complications (>10%) and potential risk factors, outcomes of fetus as well. Pearson product-moment correlation coefficient (Pearson's r) was conducted to discover the correlation between the most frequent complications.

Result: In total, 26411 pregnancies were included in the study. The incidence of six complications was over 10%, eight was 1%-10% and two was lower than 1%. Ten of fifteen complications were shown significant increases between 2001-2005 and 1976-1980. Five of six most frequent complications were related to nulliparous women. Two and three of the six

most frequent complications related to the age group ≤ 17 and ≥ 35 respectively. Hypertensive disorder was high incidence and significant related to both low birth weight and prenatal death.

Conclusions: Several of complications increased during 1973-2005 in the town of Monchegorsk. Infections of genitourinary tract, pregnant hypertensive disorders, premature rupture of membranes, abnormalities of forces of labor were shown in the higher level than in other populations over the investigated period. Especially, hypertensive disorders were higher in Monchegorsk and they had related to both low birth weight and prenatal death. Smoking using was shown in increasing trend and was an important risk factor for occurrence of complications. Women at the age between 18- 34 year-old had less pregnancy complications. Nulliparous women were at the higher risk to suffer from complications.

Insidens av vanlige komplikasjoner i svangerskapet i en kommune i Nord-Vest Russland

-En studie fra populasjonsbasert fødselsregister

Sammendrag

Formål: Dette er en populasjonsbasert fødsel studie basert på data fra Monchegorsk, som en by i den sentrale delen av Murmansk Oblast i Nordvest-Russland. De hovede målene er å fastslå utbredelsen av vanlige komplikasjoner i Monchegorsk under 1973-2005, estimere de relevante risiko faktorer for komplikasjoner, forholdet mellom komplikasjoner og analysere utfall av nyfødte.

Metode: International Classification of Disease, 10. Revisjon, koder ble brukt til å registrere komplikasjoner. Insidens av de utvalgte komplikasjoner i svangerskapet ble beskrevet. Årlig antall utvalgte komplikasjoner ble delt inn i grupper på hvert 5-år. Insidens i ulike tidsrom i 2001-2005 og 1976-1980 ble sammenlignet ved hjelp av odds ratio. Chi-Square test for uavhengighet og odds ratio har blitt gjennomført for å indikere sammenhengen mellom de hyppigste komplikasjonene (> 10%) og potensielle risikofaktorer, utfall av nyfødte. Pearson produkt-moment korrelasjon koeffisient (Pearsons r) ble utført for å finne ut hvilken korrelasjon mellom de mest hyppige komplikasjoner.

Resultat: I alt ble 26411 svangerskap inkludert i studien. Insidens av seks komplikasjoner var over 10%, åtte var 1% -10% og to var lavere enn 1%. Ti av femten komplikasjoner ble vist signifikante økninger mellom 2001-2005 og 1976-1980. Fem av seks hyppigste komplikasjoner var relatert til nulliparous kvinner. To og tre av seks hyppigste

komplikasjoner knyttet til aldersgruppen ≤ 17 og ≥ 35 henholdsvis. Hypertensiv lidelse var betydelig relatert til både lav fødselsvekt og prenatal død.

Konklusjon: Flere av komplikasjoner økte i løpet 1973-2005 i byen Monchegorsk. Infeksjoner i urin-tarmkanalen, gravide hypertensive lidelser, premature rupture of membranes, abnormalities of forces of labor ble vist på høyere nivå enn i andre populasjoner over den undersøkte perioden. Spesielt var hypertensive lidelser høyere i Monchegorsk og de hadde knyttet til både lav fødselsvekt og prenatal død. Røyking bruker ble vist i stigende trend og var viktig risikofaktor for forekomst av komplikasjoner. Kvinner i alderen mellom 18 - 34 år gammel hadde mindre svangerskapskomplikasjoner. Nulliparous kvinner var det høyere risiko for å lide av komplikasjoner.

Background

The time period from the recognition of a pregnancy until delivery is one of the greatest physical and psychological transitions that a woman undergoes in her lifetime [1]. The anatomy, physiology and metabolism are changed in nearly all tissues and organs throughout the body during this period[2, 3]. Many of the profound physiological changes occur in the cardiovascular system. Blood volumes increases early in gestation, continue to increase rapidly during the second trimester, accompanied by a rise in heart rate and change in blood pressure. Renal blood flow increasing capacity of the kidneys and ureters and renal dilation. Ventilation also increases. Both constituent cells and coagulation factors are changed in hematological system. Carbohydrate metabolism disorders are common. The gastrointestinal system changes result in gastric reflex or vomiting. In early of pregnancy, most of the changes are due to progesterone which are hormones secreted by ovaries. Along with pregnancy processes, placenta is formed. The placenta is a complex organ that facilitates nutrient and gas exchange between the mother and fetus and also serves as a barrier to protect the fetus from the maternal immune system [2-4]. Placenta has endocrine function also. Several biological factors are secreted by placenta during the different periods of pregnancy [4]. For example: Human chorionic gonadotropin, human placental lactogen: pregnancy associated plasma protein, estrogen and progesterone. The endocrine functions of placenta replace the ovarian and continue to support the pregnancy [4]. In later of pregnancy, due to the fetus and placenta growing, nutritional requirements increasing, the mother's burden increases. Enlarged uterus change the location of surrounding organs such as kidneys, heart and lungs upward, ureters are pressed and limited their physiological processes as well.

The many progressive physiological changes are important to support and protect the developing fetus and also to prepare the mother for parturition. Usually, healthy women can tolerate these changes [2, 3]. However, if these changes are over physiological tolerance

and/or there are some risk factors, that easily result in pathological damage in some tissues or organs and sometimes induce diseases, so called complications of a pregnancy. Common complications are, for example, gestational diabetes mellitus, hypertension and proteinuria, complications of labor and delivery, hemorrhage, infections of genitourinary tract. Those complications may result in big health problem in both the mothers and infants and even impact their health for their lifetime [5-7] .

Because of the differences in geography, economy and welfare systems, types of occupations, quality of prenatal care and life style vary from region to region, and also from country to country, the incidence of complications is different in the pregnant populations. The incidence of pregnant complications may also be different in the same region at different time period.

Monchegorsk is an Arctic town in north-western Russia. The Kola Birth Registry (KBR) in Monchegorsk in the Kola Peninsula of Russia was initiated in 1997[8]. The reason for the establishment of KBR was a possible increase in spontaneous abortions and structural malformations among infants of occupationally exposed female nickel workers in Monchegorsk (a nickel industry city) was reported [8, 9].

Several investigations have been done using the data in the KBR. It has been reported that the women with pregnancy were younger and had a lower prevalence of obesity and diabetes in Monchegorsk compared with Norway [10]. The prenatal mortality in the period 1973-97[8], the incidence of defects in the musculoskeletal system at birth,[11] newborn with malformations of the genital organs and some other outcomes[12] and the prevalence of anemia in pregnant women[13] had also been investigated. However, there are no comprehensive descriptions of complications relating to pregnancy in this population so far.

2. Pathophysiology and epidemiology

As mentioned above, a complication can occur any trimester of pregnancy and involve nearly all tissues and organs throughout the body. However, why and how the complications occur is not all clear yet.

Hypertensive disorders are the most common medical complications of pregnancy, affecting 5% to 22% of all pregnancies[5, 14]. The classification system recognized four major categories of this disorder: 1) gestational hypertension (hypertension occurs after 20 weeks gestation), 2) preeclampsia(gestational hypertension with proteinuria and other clinical symptoms) or eclampsia(the development of tonic clonic seizures in the setting of preeclampsia), 3) chronic hypertension(hypertension existed before pregnancy or 20 weeks gestation), and 4) preeclampsia superimposed on chronic hypertension(the development preeclampsia or eclampsia in a woman with preexisting or chronic hypertension) [5, 15, 16]. Both preeclampsia and eclampsia are serious complications of pregnancy. The risk of preeclampsia to the mother can be significant and includes the possible development of disseminated intravascular coagulation (DIC), intracranial hemorrhages, renal fail detachment, pulmonary edema, live rupture, abruption placenta, and death. The risk of preeclampsia to the fetus can become preterm delivery, fetus growth restriction, and prenatal death [5]. Diabetes mellitus is another common complication of pregnancy. In spite of the insulin was used, woman with diabetes remain at increased risk for a number of complications such as preterm labor, infections, hypertensive disorders, stillbirth, congenital malformations, childhood obesity[17]. Hemorrhage can happen throughout all of the trimester of pregnancy and result in early pregnancy loss, preterm labor, and anemia. It can also be associated with placental abruption and fetus loss if hemorrhage occurs during labor and delivery [18]. Postpartum hemorrhage (PPH) is a common cause of maternal death. Brian T. at al reported if blood loss over 500ml after vaginal delivery or over 1000ml after cesarean delivery can be defined as PPH [19]. The infections of the genitourinary track are also common medical

problems in pregnancy. They are common causes for abortion or preterm labor[20]. Acute pyelonephritis can result of fever and chills, flank pain, and varying degrees of dysuria, urgency, and frequency[21]. Premature separation of placenta, premature ruptures of membranes, long labor are common complications during the labor and delivery[22, 23]. Premature separation of placenta is an important cause of maternal death[24]. It is well known the placenta is a channel to connect mother and fetus. It delivers nutrients from mother to fetus. Any problem with placenta can impact the health of fetus.

From above descriptions we can know that pregnancy complications are very important health issues for both mothers and their fetuses. They may influence and reinforce each other. Therefore, to discover the pregnancy complications is significant to prevent and manage early.

Numerous epidemiology studies about complications of pregnancy have been done worldwide. The studies involved rate, incidence, prevalence, mortality, etiology, outcome, prevention, intervention, and management. A study has been done by a research group in United Kingdom. They found that isolated gestational proteinuria may show an early representation of preeclampsia. The risk factors were related to overweight, obesity, nulliparity, multiple pregnancy and blood pressure [25]. A report from Thailand has shown that underweight pregnant women increased the risk of maternal anemia, low birth weight, and preterm birth [26]. In China a significant increase in the prevalence of gestational diabetes mellitus in urban Chinese women has been reported [27]. An investigation about maternal mortality during 1995-2004 from Switzerland showed that the maternal mortality ratio was decreased from 5.54 to 4.15 compared to the prior 10-year period [6]. However, The frequency of PPH which was associated with substantial maternal morbidity and mortality had increased in the United States from 1995-2004 [19].

The prevention, intervention, and management of pregnant complications are very important. It can significantly reduce or avoid adverse outcomes for both mother and fetus if the complications are prevented properly and managed timely and correctly. For instance, pregnant women who suffer from urinary tract infections should be treated with antibiotics when bacteriuria is identified. The selection of antibiotics is important, the antibiotics should be safe for both the mother and fetus [28]. The prevalence of anemia in pregnant women increased from 1973 to 2002 in Monchegorsk [13] and has also remained unacceptably high worldwide, especially in developing countries over the past 30 years [29]. The iron supplement can prevent and treat the iron deficiency anemia of pregnant women has been identified [29]. Active for women with gestational diabetes mellitus may reduce rates of macrosomia and related complications [30]. There were reports had also provided methods of intervention and management for gestational diabetes mellitus and hypertensive disorders. That can improve the outcomes for both mother and fetus[31] [16].

The aim in this study is to describe the incidence of the common complications of pregnancy in Monchegorsk, North-West Russia during 1973- 2005. For the most common complications, (higher than 10%) have been tried to find risk factors and analyze the relative outcomes of fetus. It is possible to provide factual information to the local government and public health institute about some situation of woman with pregnancy in the town.

The study has three main objectives:

1. To determine the incidence of the common complications in Monchegorsk during 1973-2005.
2. To estimate what risk factors are relevant to the complications?

3. To analyze relationship between some complications and outcomes of fetus.

3. Materials and methods

3.1. Context

This is a population based birth study based on the newborn population in Monchegorsk, which a township in the central part of Murmansk Oblast (MO) in North-West Russia. Geographically most of MO is located in the north of the Polar Circle. In the year 2005, the population of MO was 873,000, of which 91.5% were living in urban settlements and 53.6% were women. From 1970 to 1990 the size of population increased. However, after 1990 the size of population of MO decreased due to emigration and also increased death and decreased birth rate. Monchegorsk is an industrial town. The largest employer has been the local nickel refinery.

Russia's basic medical insurance program provides a free prenatal care for pregnant women; it is recommended that all of the pregnant women before 12 weeks of pregnancy should visit the gynecologist for the medical care control. On 16 November 1990 a new law was promulgated, which provide a bonus to pregnant women that can get one minimum monthly wage when going on maternity leave if they consult a gynecologist before 12 weeks of pregnancy , and was obliged to leave work after week 30 of gestation with a 100% wage for the next 140 days[8].

3. 2. Population and data source

The data for this investigation is obtained from the KBR. The KBR includes extensive data about more than 98% of all lives births, as well as stillbirths of at least 28 weeks of gestation, in Monchegorsk [10]. The population included in this investigation comprised births in the period 1973–2005 by women who were registered by the KBR as residents in Monchegorsk at

the time of a pregnancy. The pregnant women were assigned an identification number so that records by the same mother can be linked, and all the data were further computably registered and administered by the Kola Research Laboratory for Occupational Health (KRLOH) in cooperation with the University of Tromsø (UiT), Norway[8]. In total, 26843 pregnancies in the period 1973-2005 were registered retrospectively. The data registered in the KBR were obtained from the medical, delivery and gynecological records of the delivering women[8]. In the study multiple pregnant (twin or more n=431) and missing (n=1) were excluded. Thus, the numbers of pregnancies included in study were 26411.

Each record in the KBR contains more than 200 fields of information about each birth. In addition to data about the newborn, the information included mothers age, height, occupation; civil status, the first time to visit gynecologist for pregnancy; the diseases and medical using history of mother unrelated to pregnancy, pregnancy; delivery; tobacco and alcohol abuse; all kind of complications during the pregnancy. The age of mother was obtained from first visit with gynecologist. It is recorded in years. The information of complications was recorded in different fields with ICD-10 code and word or string. That means that more than one complication could be registered for each pregnancy and delivery. Information of smoking and alcohol abuse were recorded with Yes or No. The birth weight of fetus was recorded with gram. Prenatal death was recorded with stillborn and days of child died after delivery[8]. The name, age, occupation and employer of the father are also registered.

KBR has used ICD-code 10 (International Classification of Diseases, Organized by the WHO, 10th revision) to recode recorded complications of pregnancy. The complications included in this study were selected from ICD-code 10, chapter15 [Pregnancy, childbirth and the puerperium (O00-O99)]. These complications include the maternal complications during the pregnancy; other maternal disorders predominantly related to pregnancy; the amniotic cavity

and possible delivery problems and complications of labor and delivery. They are outlined in table1:

Table1: The complications of pregnancy and delivery selected for the investigation, based on the coding in the International Classification of Disease (ICD-10)

Category	ICD-10 code	Complication
Gestational hypertension and proteinuria	O12	Gestational edema and proteinuria without hypertension
	O13	Gestational hypertension without significant proteinuria
	O14	Gestational hypertension with significant proteinuria
	O15	Eclampsia
	O16	Unspecified maternal hypertension
Other maternal disorders predominantly related to pregnancy	O21	Excessive vomiting in pregnancy
	O23	Infections of genitourinary tract in pregnancy
	O24.4;O24.9	Gestational Diabetes mellitus; Unspecified diabetes mellitus in pregnancy
The amniotic cavity and possible delivery problems	O40	Polyhydramnios
	O42	Premature ruptures of membranes
	O43	Placental disorders
	O44	Placenta previa
	O45	Premature separation of placenta
	O48	late pregnancy
Complication of labor and delivery	O62	Abnormalities of forces of labor
	O72	Postpartum hemorrhage
	O73	Retained placenta and membranes, Without hemorrhage

3.3. Data analyses

SPSS version 19 software was used for the statistical analysis. The selected complications for the analysis from the primary data were a mixture of 3-digit and 2-digit levels in different fields. In the first step, the data of complications were transferred from 3-digit level (ICD-10 coding.) into 2-digit level by using transform function of SPSS (For example O12.1+O12.2+O12.3=O12). The same complications in different columns were gathered in one column by using transform and compute variable function of SPSS. Mother's characteristics and the number and percentage of the complications with 95% confident interval were presented in table. Annual number of total pregnancies and each selected complication were conducted by using compare main function of SPSS. And then, the data was divided into groups of every 5-year, the incidence in different time period at 2001-2005 and 1976-1980 was compared by using odds ratio (OR). A Chi-Square test for independence and odds ratio has been conducted to analyze the association between potential risk factors and the most frequent complications. Some complications that have similar clinical significance were analyzed as one group: gestational hypertension without significant proteinuria, gestational hypertension with significant proteinuria and unspecified maternal hypertension (from here labeled the hypertensive disorders).

Chi-square analyses were also conducted to examine the relationship between complications and outcomes of fetus. The low birth weight (LBW) and prenatal death were included in analysis. Newborn's birth weights with and lower than 2500 gram would be included in the low birth weight group. Stillbirths and child who died within 7 days after delivery were defined as prenatal death. Pearson product-moment correlation coefficient (Pearson's r) was conducted to discover the correlation between the most frequent complications.

Statistical significance level was tested at 95 % ($p < 0.05$).

4. Results

The Characteristics of the pregnancies (n=26411) and information of risk factors are shown in table2. Most of mothers were 18-34 years old (n=24374, 92.3%). The pregnancies which had null and one parity were 13827(52.4%) and 9810(37.2%) respectively. There were 142(0.50%) of pregnancies with alcohol and 491(1.9%) with tobacco.

Table2: Maternal Characteristics and information of risk factors

Maternal Characteristics	number	Percentage
Age		
≤17	568	2.15
18-34	24374	92.29
≥35	1469	5.56
Parity*		
0	13827	52.35
1	9810	37.14
≥2	2766	10.47
Missing	8	0.03
Alcohol		
Yes	142	0.50
No	26265	99.45
missing	4	0.02
Tobacco		
Yes	491	1.86
No	25915	98.12
missing	5	0.02

*Parity 0=nulliparity, Parity 1 =one previous delivery, Parity ≥2= More than one previous delivery

The frequency and incidence of each complication are presented in Table3. The incidence of complications was less than 10% for most of them. The highest incidence (over 10%) were found for gestational edema and proteinuria without hypertension (ICD10-O12, 25.8%), gestational hypertension without significant proteinuria (ICD-O13, 13.2%), excessive

vomiting in pregnancy (ICD10-O21, 11.4%), infections of genitourinary tract in pregnancy (ICD10-O23, 20.3%), premature ruptures of membranes (ICD10-O42, 24.1%) and abnormalities of forces of labor (ICD10-O62, 23.7%). The lowest were for eclampsia(ICD10-O15, <0.1%) and gestational diabetes mellitus and unspecified diabetes mellitus in pregnancy (ICD-10 O24.4; O24.9, 0.1%), and the numbers of pregnancies with these two complications were only 8 and 32 respectively.

Table3: The number and incidence with 95% confidence interval* (95%CI) of selected complications during 1973-2005

ICD10-code	number	Percentage(95%CI)
O12	6804	25.8(25.3-26.3)
O13	3488	13.2(12.8-13.6)
O14	487	1.8(1.7-2.0)
O15	8	0.03(0.00-0.10)
O16	2051	7.8(7.4-8.1)
O21	3022	11.4(11.1-11.8)
O23	5364	20.3(19.8-20.8)
O24.4, 24.9	32	0.1(0.10-0.20)
O40	1364	5.2(4.9-5.4)
O42	6370	24.1(23.7-24.7)
O43	854	3.2(3.0-3.5)
O44	345	1.3(1.2-1.5)
O45	617	2.3(2.2-2.5)
O48	235	0.9(0.8-1.0)
O62	6247	23.7(23.2-24.2)
O72	556	2.1(1.9-2.3)
O73	459	1.7(1.6-1.9)

*Conducted by using of SPSS: Descriptive statistics >Frequencies> Bootstrap. The results based on 1000 bootstrap.

The average incidence of complications at every 5-year period from 1973 to 2005 (except for 1973-75) is presented in table4.

The difference between 1976-1980 and 2001-2005 are also presented in table 4. The data indicated that the majority of all complications had a significant increasing (OR >1, p <0.001). polyhydramnios and placental disorders had shown larger odds ratio (6.41, 17.77) respectively and placental disorders shown also large 95%CI (9.27-34.03).

Table4: Incidences of the complications in different time period (%) and difference between the periods 2001-2005 and 1976-1980(Odds ratio):

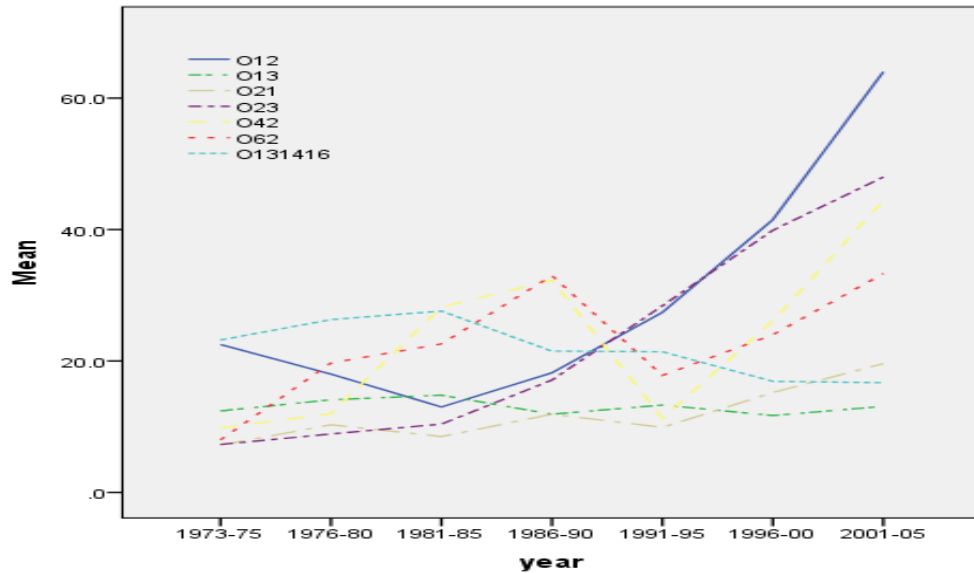
ICD-10 code	1973-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	Difference between the periods 2001-2005 and 1976-1980	
								Odds ratio#(95%CI) *	P
O12	22.51	18.0	13.0	18.2	27.4	41.5	64.0	3.58(3.24-3.91)	<0.001
O13	12.38	14.1	14.8	11.9	13.3	11.7	13.1	0.93(0.82-1.07)	0.314
O14	2.60	1.6	1.5	1.3	2.6	2.0	2.5	1.53(1.10-2.11)	<0.001
O16	8.25	10.6	11.4	8.4	5.4	3.2	1.1	0.10(0.07-0.14)	<0.001
O21	7.62	10.3	8.5	11.9	9.9	15.2	19.6	1.92(1.69-2.18)	<0.001
O23	7.31	8.9	10.4	17.1	28.4	39.9	48.0	5.40(4.80-6.08)	<0.001
O24.4;O24.9	0.1	0.0	0.0	0.1	0.3	0.1	0.4		
O40	1.00	2.6	2.6	4.4	3.4	9.8	16.7	6.41(5.23-7.85)	<0.001
O42	9.78	12.0	28.2	32.3	11.3	26.1	44.4	3.69(3.31-4.12)	<0.001
O43	1.26	0.2	0.4	0.5	11.6	11.2	4.1	17.77(9.27-34.03)	<0.001
O44	1.12	0.7	0.5	0.7	4.7	2.4	1.3	0.94(0.52-1.68)	0.842
O45	1.21	1.5	1.5	1.6	3.1	4.4	4.9	3.21(2.41-4.29)	<0.001
O48	0.72	0.04	1.08	1.37	0.28	0.38	0.62	2.76(1.80-4.24)	<0.001
O62	8.03	19.7	22.6	33.0	17.8	24.0	33.3	1.69(1.53-1.87)	<0.001
O72	5.00	2.4	2.4	1.8	0.9	1.4	1.3	0.54(0.37-0.78)	0.001
O73	2.70	1.2	1.3	2.1	1.9	2.4	1.3	1.01(0.66-1.54)	0.958
O13,O14,O16	23.2	26.3	27.6	21.5	21.4	16.9	16.7	0.63(0.57-0.71)	<0.001

#Odds ratio was estimated by using average of number of complication and total number of deliveries between 2001-2005 and 1976-1980, respectively.

*95% confidence interval

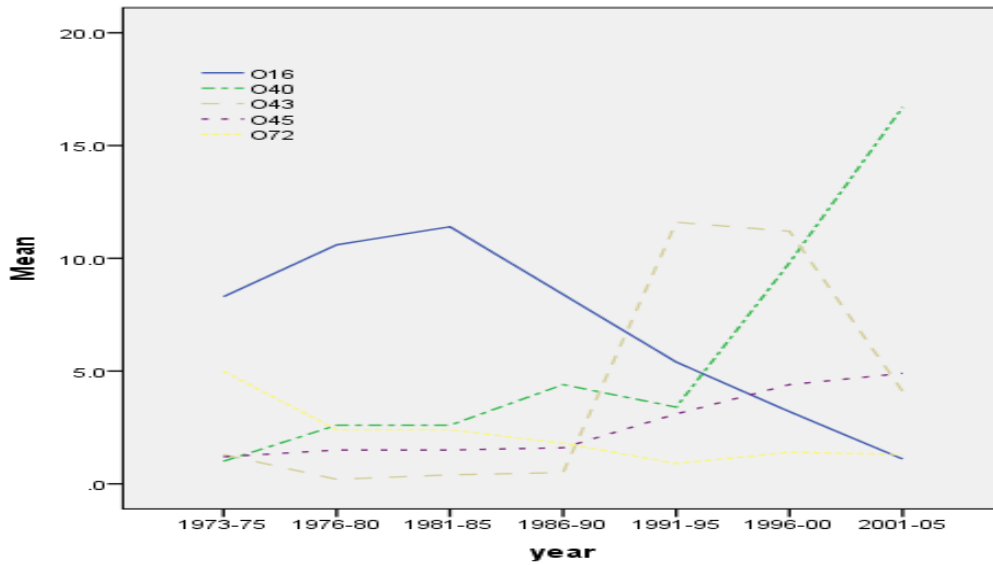
Overviews of incidence changes from 1973 to 2005 are shown in Figures 1, 2 respectively.

Figure 1: The selected complications of pregnancy which had incidence more than 10%



Legend to Figure 1: O12, O23 was quickly increased from 1981-1985 periods. O42 and O62 were shown unstable status and were continuous increased from 1991-1995. The hypertensive disorders had a gradual decrease trend from 1981-1985.

Figure2: The selected complications of pregnancy which had incidence were between 2% to 10%



Legend to Figure2: Both O16 and O72 were decreased and O16 was quickly decreased from 1981. O45 was gradual increased since 1986-1990. O40 had a light wave and was increased quickly since 1991-1995. O43 had a sharp and remarkable increase (11, 6% and 11.2%) at the period of 1991-1996.

The age ≤ 17 year-old was a significant risk factor for gestational edema and proteinuria without hypertension (ICD10-O12, OR 1.34) and infections of genitourinary tract in pregnancy (ICD10-O23, OR 1.96). The age ≥ 35 was a significant risk factor in gestational hypertension without proteinuria (ICD10-O13, OR 1.6), premature ruptures of membranes (ICD10-O 42, OR 1.16) and the hypertensive disorders (ICD10-O13, O14, O16, OR 1.6). Nulliparity was a significant risk factor in all of the complications except for abnormalities of forces of labor (ICD10-O62). The abnormalities of forces of labor (OR 1.15) and hypertensive disorders (OR1.11) were significant associated with parity ≥ 2 . Alcohol abuse was only significant association with the hypertensive disorders (OR1.47) .Tobacco use was a significant risk factor for gestational edema and proteinuria without hypertension (OR 2.71), premature ruptures of membranes (OR, 1.73) and abnormalities of forces of labor (OR 1.53). All of the results were shown in table5.

Table5: Potential risk factors for different complications

ICD-10	Age≤17	Age18-34	Age≥35	Parity=0	Parity=1	Parity≥2	Alcohol	Tabacco
O12								
χ^2 \square	10.04	0.69	8.85	135.30	46.53	67.21	8.99	127.89
p-value	0.002	0.41	0.003	0.000	0.000	0.000	0.003	0.000
OR#	1.34 (1.12-1.60)	1.05 (0.95-1.16)	0.83 (0.73-1.94)	1.39 (1.32-1.47)	0.82 (0.77-0.87)	0.66 (0.60-0.73)	0.50 (0.31-0.79)	2.71 (2.26-3.24)
(95%CI)*								
O13								
χ^2	1.01	28.22	46.51	23.40	31.23	0.86	0.004	1.75
P-value	0.315	0.000	0.000	0.000	0.000	0.354	0.951	0.186
OR (95%CI)	0.88 (0.68-1.13)	0.72 (0.64-0.81)	1.60 (1.39-1.83)	1.19 (1.11-1.28)	0.81 (0.75-0.87)	1.06 (0.94-1.18)	1.02 (0.63-1.65)	0.83 (0.62-1.10)
O13,14,16								
χ^2	4.77	30.35	60.75	32.17	53.17	5.07	4.52	6.25
P-value	0.029	0.000	0.000	0.000	0.000	0.024	0.034	0.012
OR (95%CI)	0.79 (0.64-0.98)	0.75 (0.68-0.83)	1.57 (1.40-1.76)	1.18 (1.12-1.25)	0.80 (0.75-0.85)	1.11 (1.01-1.22)	1.47 (1.03-2.11)	0.74 (0.59-0.94)
O23								
χ^2	57.06	2.71	44.85	494.00	293.69	84.62		
P-value	0.000	0.100	0.000	0.000	0.000	0.000		
OR (95%CI)	1.96 (1.64-2.34)	1.10 (0.98-1.24)	0.60 (0.51-0.70)	2.20 (1.90-2.15)	0.56 (0.53-0.60)	0.59 (0.53-0.66)		
O42								
χ^2	6.64	0.40	5.60	20.99	8.87	7.68	0.002	33.80
P-value	0.010	0.528	0.018	0.000	0.003	0.006	0.961	0.000
OR (95%CI)	0.76 (0.62-0.94)	0.97 (0.87-1.07)	1.16 (1.03-1.30)	1.14 (1.08-1.21)	0.92 (0.86-0.97)	0.88 (0.80-0.96)	0.99 (0.67-1.46)	1.73 (1.44-2.09)
O62								
χ^2	1.35	3.65	2.21	1.00	0.83	9.39	0.10	19.19
P-value	0.250	0.056	0.137	0.317	0.363	0.002	0.753	0.000
OR (95%CI)	1.12 (0.93-1.35)	0.90 (0.81-1.00)	1.10 (0.97-1.24)	0.97 (0.92-1.03)	0.97 (0.92-1.03)	1.15 (1.05-1.26)	0.94 (0.63-1.39)	1.53 (1.26-1.85)

$\square \chi^2$ =Chi-Square #OR= Odds Radio *95%CI=95% confidence interval

The correlations between the most common complications were presented in table 6. Positive significant correlations were found between gestational edema and proteinuria without

hypertension (ICD10-O12)(Pearson's r 0.68) and infections of genitourinary tract in pregnancy (ICD10-O23), premature ruptures of membranes (ICD10-O42) and abnormalities of forces of labor (ICD10-O62)(Pearson's r 0.752)

Table 6: The correlations between the most common complications

	O12	O13	O14	O23	O42	O62
O23						
Pearson's r	0,680	-0,360	-0.167		0.232	0.086
p	0,000	0,040	0.353		0.195	0.635
O42						
Pearson's r	0,191	0.131	-0.090			
p	0.288	0.469	0.619			
O62						
Pearson's r	0,156	0.274	0.065	0.086	0.752	
p	0.385	0.123	0.721	0.635	0.000	

The associations between the most common complications and the perinatal outcomes were shown in table7. Significant positive associations were found between the hypertensive disorders and both lower birth weight (OR 1.27) and perinatal death (OR 1.34). Especially, gestational hypertension with significant proteinuria (ICD10-O14) was shown high risk for both lower birth weight (OR4.41) and perinatal death (OR 4.17).

Table 7: The associations between outcomes of the fetus and the most frequent complications

	Low birth wight			Perinatal death		
	χ^2	P-value	OR(95%CI)*	χ^2	p-value	OR(95%CI)
O12	160.21	0.000	0.42(0.37-0.49)	41.29	0.000	0.43(0.33-0.56)
O13	3.00	0.083	0.88(0.76-1.02)	0.89	0.345	1.13(0.88-1.45)
O14	220.64	.000	4.41(3.57-5.47)	71.11	0.000	4.17(2.91-6.00)
O13,14,16	19.01	0.000	1.27(1.14-1.41)	8.41	0.004	1.34(1.10-1.63)
O23	16.48	0.000	0.77(0.68-0.87)	9.98	0.002	0.67(0.52-0.86)
O42				6.88	0.002	0.74(0.59-0.93)
O62				3.46	0.063	0.81(0.65-1.01)

χ^2 =Chi-Square

* OR (95%CI) = Odds Ratio (95% confidence interval)

5. Discussion

This investigation has selected more than 16 complications of pregnancy to study the incidence, risk factors, and relationship between common complications of the pregnancy and newborn outcomes in a town of Monchegorsk, in North-West Russia, during 1973-2005 based on the data registered in the local birth register.

5.1 The most frequent complications (incidence over 10%)

5.1.1. Gestational edema and proteinuria without hypertension

Gestational edema and proteinuria without hypertension was a most frequent complication of the pregnancy in this investigation. The highest incidence was 64% which was at the year-period of 2001-2005. A quickly increase was found since the years 1991-1995. The risk factors of gestational edema and proteinuria without hypertension were associated with the younger (≤ 17 year-old) woman, nulliparity and tobacco using in pregnancy.

Mackay DF. et al had reported that smoking during pregnancy and maternal exposure to environmental tobacco smoke can increase the risk of pregnancy complications [32]. The prevalence of tobacco using in pregnant women was 1.9% in the town of Monchegorsk. That was increased 2-fold as compared with the rate (0.7%) reported from the same area in the period of 1973-1997 [10], but much lower than Scotland (25.4%-18.8%) [32] and a cohort study in Norway(10.9%)[33].

The investigation had also found that there was strong correlation between gestational edema and proteinuria without hypertension and infections of genitourinary tract in pregnancy (Pearson's r 0.680). Accord to effect size which was suggested by Cohen[34]: small $r=0.1$ to 0.29, medium $r=0.30-0.49$. Lager $r=0.50-1.0$. It was lager effect lever of positive correlation.

That indicate the gestational edema and proteinuria are maybe a risk factor for infections of genitourinary tract in pregnancy.

Edema is a nonspecific finding of many diseases. Any causes which result of unbalance between intracellular and extracellular of the body, they can also result of edema. Usually, lower extremity edema can affect 80%[35] or can be found almost all of the pregnancy[36]. Most of the pregnancy edema occurs from second trimester. Several factors conducive to edema formation are, such as increased plasma volume, hypertension, protein loss, local infection[37]. For the gestational edema and proteinuria without hypertension, protein loss is an important factor. It had not much investigation for only edema of a pregnancy because the most edema of pregnancy has no influence for women health. It is disappear quickly after childbirth. However, there have been reported the cases of maternal death associated with severe postpartum vulvar edema[38]. Edema and proteinuria can result of and/or accompany serious diseases. Therefore, it should not be ignored at any time.

5.1.2. Gestational hypertension without significant proteinuria and the hypertensive disorders

Gestational hypertensive disorders are a series of common and serious complications of the pregnancy. It affects the pregnancy varied from 5% to 22% from different reports [5, 14, 16]. Many studies have been done in this field. That included incidence, prevalence, mortality, etiology and outcome. In this investigation, the incidence of gestational hypertension without significant proteinuria (ICD10-O13) was 13.2%. The hypertensive disorders (ICD10-O13, O14, and O16) were 22.8%. However, the pre-existing hypertension complicating pregnancy (ICD-10-O10) and the pre-existing hypertensive disorder with superimposed proteinuria (ICD10-O11) were excluded in this study. If all types of the hypertensive disorders were added together, the incidence of total hypertensive disorders were up to 24.3% (data not

shown). It indicated that the incidence of hypertensive disorders of pregnancy were higher in the town of Monchegorsk. Although it was shown decreases trend over the time, the incidence at the period of 2001-2005 was 16.7%, which is still at a higher level. The risk factors related to hypertensive disorder were age (≥ 35), parity (nulliparity, parity ≥ 2 as well), alcohol abuse during pregnancy.

Some investigations had found that the age of pregnant women was related to the occurrence of the complications [5, 10]. They have revealed that the age group above 34 and 13-17 are increased risk for both mother and fetus and the women who were older than 35 have high risk for gestational hypertensive disorder. This is similar with our study.

The nulliparous women have high risk for gestational hypertensive disorder had been reported [5, 25]. The multiparous women had also been shown in high risk in our study. This result maybe affect by age confounding.

The rate of alcohol abuse with pregnancy was 0.5% in this investigation. It is consisted with the previous report [10]. Alcohol associate to the development of hypertension had been reported[39]. Because of the data contain not high (0.5%) proportion of the alcohol abuse with pregnancy of KBR, therefore, the result should be confirm in future. In spite of alcohol using is a risk factor for both mother and fetus in many reports [40-42]. However, it is not an important risk factor for the pregnant women in Monchegorsk because of lower rate of alcohol abuse.

Gestational hypertension with significant proteinuria (ICD10-O14) is a serious complication of pregnancy. According to the definition of ICD-10, it is equal preeclampsia. The incidence of gestational hypertension with significant proteinuria was 1.8% in this investigation. This is

lower than Norway (2%)[43] and USA (2-7%) [5]. However, it was significantly increased over the time period in this area (Monchegorsk). This must be taken attention to.

The gestational hypertension without significant proteinuria (ICD10-O13) had shown insignificant association with LBW and prenatal death, while the hypertensive disorder (ICD10-O13, 14, 16), especially, gestational hypertension with significant proteinuria (ICD10-O14), had shown significant association with both of them. This result indicated that the gestational hypertension with significant proteinuria (ICD10-O14) was a main cause for both LBW and prenatal death. Because of the numbers of eclampsia (ICD10-O15) was only 8 in the investigation period. It was not analyzed the outcomes of fetus in this study.

5.1. 3. Infections of genitourinary tract in pregnancy

Infections of genitourinary tract in pregnancy are also a series of complications of the pregnancy. In this investigation, it affected 20.3% of all the pregnant women. The highest incidence was 48% that was at the year-period of 2001-2005. The rate of infections of genitourinary tract was increased over the time and a remarkable increase trend was found since 1991-1995 (from 28.4% to 48%). This was much high than the infection rate recently reported from two American studies (11% and 12.9% respectively)[21, 44]. The risk factors of infections of genitourinary tract in pregnancy have been found to be associated with the younger (≤ 17 years old) woman, nulliparous women in this investigation. Whereas Charles et al. found that increasing parity is a risk factor of infections of genitourinary tract in pregnancy[21]. This perhaps due to some confounding which were involute in different studies, for example, age or history of urinary tract infections of studies populations. As mentioned early, there was a strong correlation between gestational edema and proteinuria without hypertension and infections of genitourinary tract in pregnancy. The gestational edema and proteinuria may also be the risk factors for infections of genitourinary tract in

pregnancy. It has been reported that the infections of genitourinary tract in pregnancy can result in or worse the edema of pregnancy [36, 37]. Thus, it is speculated that they can cause and reinforce each other during the pregnancy. Another report had shown that infections of genitourinary tract had higher risk for low birth weight[45]. But, we could not confirm it in our present study.

Regarding the pathogenesis of urinary tract infections, many factors may contribute to the development of urinary tract infections during pregnancy. Ureteral dilatation, increased bladder volume and decreased bladder tone contribute to increased urinary stasis and ureterovesical reflux. Physiological increased in plasma volume and decreased urine concentration which encourages bacterial growth in the urine. Increases in urinary progesterin and estrogens may lead to a decreased ability of the lower urinary tract to resist invading bacteria [45]. The organisms that cause infections of genitourinary tract during pregnancy are mainly *Escherichia coli*. But the percentage were varied in the different report from 41.9 % [46] to 80-90% [45]. The data in KBR are only record with *Yes* or *No* and without location and organisms. Those are limited for study in the future.

5.1.4. Premature rupture of membranes

Premature rupture of membranes is the rupture of the fetal membrane before labor. It is common problem of obstetrics. Usually, premature rupture of membranes affect in approximately varied 5%-12% of pregnant women[47, 48]. The incidence of premature rupture of membranes was 21.4% in this study and much higher than those reports. The cause of premature rupture of membranes is not clearly understood yet. It has been reported that three factors were associated with occurrence of premature rupture of membranes. They were previous preterm deliveries, smoking during pregnancy and bleeding. Particularly, bleeding in third trimester is a high risk factor[47]. Infection of fetal membrane and local defect in

membrane are also relevant to occurrence of premature rupture of membranes[48]. In this study, identified risk factors were smoking during pregnancy, age ≥ 35 and nulliparity. Why the incidence of premature rupture membranes was so high in Monchegorsk is unclear.

5.1.5. Abnormalities of forces of labor

Abnormalities of forces of labor are common complications during labor. It is because of inadequate or uncoordinated uterine contraction result of obstructed labor. Obstructed labor is important cause of maternal and fetal mortality and morbidity[49]. The causes of inadequate or uncoordinated uterine contraction during labor are multiply and understood unclear. It has been reported in an animal study that oxytocin and vasopressin concentrations is lower in the dystocia dogs than in the control dogs, which may be related to the pathophysiology of total primary uterine inertia in bitches[50]. Another report from UK had also shown that obesity may impair the ability of the uterus to contract in labor[51]. The rate of labor abnormalities was 25% to 30% of nulliparous women and in 10% to 15% multiparous women[22]. However, there were few reports about only abnormalities of forces of labor.

In this study, the incidence of abnormalities of forces of labor was generally increased with a rate of 23.7%. However, the rate over the investigated period was unstable and changed from year to year. The risk factors related to abnormalities of forces of labor were parity ≥ 2 and smoking during pregnancy. It has also been found that the premature rupture of membranes was larger size correlation with abnormalities of forces of labor (Pearson's r 0.752). That indicates the premature rupture of membranes is maybe a risk factor for abnormalities of forces of labor.

It is not understood why the abnormalities of forces of labor had shown in a larger unstable status. The reasons maybe: 1. the premature rupture of membranes influence the abnormalities

of forces of labor because it was strong correlation between them. 2. Diagnose bias, because labor abnormalities do not only be abnormalities of forces of labor, but also the other. That maybe also can explain why the risk factor was nulliparous women in other report while the one of the risk factor for abnormalities of forces of labor was multiparous women in our study. 3. Age group was different in the different period.

It was insignificant between the abnormalities of forces of labor and prenatal death in our investigation. It is well known that cesarean operation can change the process for both labor and delivery of pregnancy. It can also change the outcomes of both the mothers and the fetuses. The information was from a report that the cesarean delivery rate was increased from 5% to 30% from 1970 to 2005 in USA. The indication of cesarean delivery included all of the abnormalities that occur in women during delivery[22]. However, it could not know that how many women with abnormalities of forces of labor was performed cesarean from data of KBR.

5.2. The other selected complications

The incidences of eight complications were shown between 1% and 10% in this study. The result did not been compared with other population.

The two of complications (eclampsia, gestational diabetes mellitus and unspecified diabetes mellitus) were with low incidence (< 1%). They are two serious complications of pregnancy. The rate of eclampsia in different countries was varied. It was 0.05% to 0.1% in USA, but was much higher in the developing country [5]. Compared with these data, our data was lower. In the present investigation, only the gestational diabetes mellitus and unspecified diabetes mellitus in pregnancy were included, as compared prevalence of gestational diabetes mellitus women in China(2.4 to 6.8%) [27], women in USA(5%)[17] and woman in Norway (1.4%) in

2009(data from the website of folkehelseinstituttet, Norway), the incidence level of gestational diabetes mellitus in Monchgorsk was lower (0.1%).

The majority of pregnancy complications were shown increases trends during the past 33 years. Our result was similar to a report from USA, in which several complications of pregnancy have been shown in increasing of medical encounter from 2001-2010 [44]. The incidence of complications was varied from complication to complication and from period to period. For this reason, odds ratio was conducted and the incidence change was compared during 1980-1986 and 2001-2005(excluded gestational diabetes mellitus and unspecified diabetes mellitus) (table 4) where had shown that ten of fifteen (accounted for 66.7%) complications were significant increased. Because of gestational diabetes mellitus and unspecified diabetes mellitus in pregnancy had lower number of the frequency; the odds ratio was not conducted. But it could be said the increase trend from percentage (table4) (0.1%-0.4%).

Why a number of complications were increase are unclear. It is speculated that multiple factors involved in their occurrence. It was maybe a cause that the increases in the number of pregnant women to visit the gynecologist for the medical care control .Because of the new law was promulgated since 1990 so that they have good bonus to visit the gynecologist. The rate of diagnosis had increase along with increasing lever of medical care, for example, some pregnant women only were with asymptomatic bacteriuria[45]. Changed the lifestyles, food ingredient, age group and reduced activity of outdoor [30], population changed due to emigration after 1990[10] were also affected the occurrence of pregnant complications. In addition, the data used was during 1973-2005, but KBR was initiated in 1997. Information biases have to concern.

6. Strengths and limitations of the study

6.1 Validity/reliability

The data set of KBR is a comprehensive population-based birth registry. The data entering procedure is very strictly. There was two staff at the Kola Research Laboratory for Occupational Health (KRLOH) who sat by the computer together for data gathering from medical records and importation, cross checks accompany as well. The leader of the KRLOH performed random checks[8]. The ICD-10 cord was used for disease record and classification. These make a high standard. The information in KBR was obtained from the medical, delivery and gynecological records. The information of the medical, delivery and gynecological records was obtained from questions between the gynecologist and the pregnant women, the clinical examinations as well. The study covered all of the pregnancy (26411) and over 33 years in the town of Monchegorsk. It ensure that the information have high reliability.

Because of more than 16 complications were involute in this study, the complications were analyzed by only using Chi-Square test for each complication and each risk factor. The analyses were not adjusted for maternal age. Therefore, some results affected by age confounding. It is better to adjust the age for complication one by one in the future studies.

As mention early, the period of this study lasted 33 years so that information and diagnose bias must be concerned to.

6.2. The limitations

Alcohol abuse and tobacco use in pregnancy was likely under-recorded. The recorded information was based on clinical observation or communication by the pregnant woman.

Thus, the possible effects or associations of alcohol use and smoking in pregnancy on the risk of complications were likely underestimated.

Some information of complications, for instance, gestational edema and proteinuria without hypertension, in the KBR did not been localization and classification. Infections of genitourinary tract in pregnancy were without location and organisms. Gestational diabetes mellitus and unspecified diabetes mellitus were without the level of blood glucose and glycosuria and the time of occurrence. The pre-existing diabetes mellitus and other endocrine diseases were recorded in the same filed. It was limited to study the all types of gestational diabetes mellitus.

There was no information of following up for mother after birth in the KBR. It was limited to study the outcomes of the mothers.

7. Conclusion

This study has revealed that the several of complication increased during 1973-2005 in the town of Monchegorsk. Infections of genitourinary tract, pregnant hypertensive disorders, premature rupture of membranes, abnormalities of forces of labor were shown in the higher level than in other populations over the investigated period. Especially, hypertensive disorders were higher in Monchegorsk and they had related to both LBW and prenatal death. Smoking using was shown in increasing trend and was an important risk factor for occurrence of complications. Women at the age between 18- 34 year-old had less pregnancy complications. Nulliparous women were at the higher risk to suffer from complications. Choosing the best age for becoming pregnant, enhancing perianal care for nulliparous women and stopping smoking are significant to prevent and reduce complications of pregnancy.

8. Reference:

1. Katz. VL. Prenatal Care. In: *Danforth's Obstetrics and Gynecology*. Edited by Gibbs Rs. 10 ed; 2008. pp. 1-21.
2. Carlin A, Alfirevic Z. Physiological changes of pregnancy and monitoring. *Best Practice & Research Clinical Obstetrics and Gynaecology* 2008,**22**:801-823.
3. Rosen SRGaMA. Anesthetic Implications of Maternal Physiological Changes During Pregnancy. *Seminars in Anesthesia, Perioperative Medicine and pain* 2000,**19**:1-9.
4. Rawn SM, Cross JC. The Evolution, Regulation, and Function of Placenta-Specific Genes. In: *Annual Review of Cell and Developmental Biology*. Palo Alto: Annual Reviews; 2008. pp. 159-181.
5. M HMSB. Hypertensive Disorders of Pregnancy. In: *Danforth's Obstetrics and Gynecology*. Edited by al.] RsGE. 10 ed; 2008. pp. 257-275.
6. Fassler M, Zimmermann R, Quacklotscher KC. Maternal mortality in Switzerland 1995-2004. *Swiss medical weekly* 2010,**140**:25-30.
7. Helgadottir LB, Skjeldestad FE, Jacobsen AF, Sandset PM, Jacobsen EM. Incidence and risk factors of fetal death in Norway: a case-control study. *Acta Obstet Gynecol Scand* 2011,**90**:390-397.
8. Vaktskjold A, Talykova L, Chashchin V, Nieboer E, Odland JO. The Kola Birth Registry and perinatal mortality in Moncegorok, Russia. *Acta Obstet Gynecol Scand* 2004,**83**:58-69.
9. Chashchin VP, Artunina GP, Norseth T. Congenital defects, abortion and other health effects in nickel refinery workers. *The Science of the total environment* 1994,**148**:287-291.
10. Vaktskjold A, Paulsen EE, Talykova L, Nieboer E, Odland JO. The prevalence of selected pregnancy outcome risk factors in the life-style and medical history of the delivering population in north-western Russia. *International journal of circumpolar health* 2004,**63**:39-60.
11. Vaktskjold A, Talykova LV, Chashchin VP, Odland JO, Nieboer E. Maternal nickel exposure and congenital musculoskeletal defects. *American journal of industrial medicine* 2008,**51**:825-833.
12. Vaktskjold A, Talykova LV, Chashchin VP, Nieboer E, Thomassen Y, Odland JO. Genital malformations in newborns of female nickel-refinery workers. *Scandinavian journal of work, environment & health* 2006,**32**:41-50.
13. Chumak EL, Grijbovski AM. Anemia in pregnancy and its association with pregnancy outcomes in the Arctic Russian town of Monchegorsk, 1973-2002. *International journal of circumpolar health* 2010,**69**:265-277.

14. Charles R.B. Beckmann FWL, Barbara M. Barzansky, William N.P. Herbert, Douglas W. Laube, Roger P. Smith. Hypertension in pregnancy. In: *Obstetrics and Gynecology*. Edited by Laube DW. 6th ed ed. Lippincott Williams & Wilkins, a Wolters Kluwer business; 2010. pp. 175-181.
15. Maloney KF, Heller D, Baergen RN. Types of Maternal Hypertensive Disease and Their Association with Pathologic Lesions and Clinical Factors. *Fetal Pediatr Pathol* 2012.
16. National High Blood Pressure Education Program Working Group on High Blood Pressure in P. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics and Gynecology* 2000,**183**:S1-S22.
17. J REAHC. Diabetes Mellitus and pregnancy. In: *Danforth's Obstetrics and Gynecology*. Edited by al.] RsGE. 10 ed; 2008. pp. 246-256.
18. Huq FY, Kadir RA. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. *Haemophilia : the official journal of the World Federation of Hemophilia* 2011,**17 Suppl 1**:20-30.
19. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesthesia and analgesia* 2010,**110**:1368-1373.
20. Charles R.B. Beckmann FWL, Barbara M. Barzansky, William N.P. Herbert, Douglas W. Laube, Roger P. Smith. Preterm Labor. In: *Obstetrics and gynecology*. Edited by Gynecologists TACoOa. 6 ed: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2010. pp. 201-205.
21. Charles R.B. Beckmann FWL, Barbara M. Barzansky, William N.P. Herbert, Douglas W. Laube, Roger P. Smith. Pelvic Support Defects, Urinary Incontinence, and Urinary Tract Infection In: *Obstetrics and Gynecology*. 6th Edition ed; 2010. pp. 259-268.
22. D DJ. Complications of Labor. In: *Danforth's Obstetrics and Gynecology*. Edited by al.] RsGE. 10 ed; 2008. pp. 431-451.
23. R GLCYE. Complications of Delivery. In: *Danforth's Obstetrics and Gynecology*. Edited by al.] RsGE. 10 ed; 2008. pp. 452-461.
24. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. *Acta obstetrica et gynecologica Scandinavica* 2011,**90**:140-149.
25. Macdonald-Wallis C, Lawlor DA, Heron J, Fraser A, Nelson SM, Tilling K. Relationships of risk factors for pre-eclampsia with patterns of occurrence of isolated gestational proteinuria during normal term pregnancy. *PloS one* 2011,**6**:e22115.
26. Liabsuetrakul T. Is international or Asian criteria-based body mass index associated with maternal anaemia, low birthweight, and preterm births among Thai population? An observational study. *Journal of health, population, and nutrition* 2011,**29**:218-228.
27. Zhang F, Dong L, Zhang CP, Li B, Wen J, Gao W, et al. Increasing prevalence of gestational diabetes mellitus in Chinese women from 1999 to 2008. *Diabetic medicine : a journal of the British Diabetic Association* 2011,**28**:652-657.
28. Lee M, Bozzo P, Einarson A, Koren G. Urinary tract infections in pregnancy. *Can Fam Physician* 2008,**54**:853-854.

29. Mungen E. Iron supplementation in pregnancy. *J Perinat Med* 2003,**31**:420-426.
30. Witkop CT, Neale D, Wilson LM, Bass EB, Nicholson WK. Active compared with expectant delivery management in women with gestational diabetes: a systematic review. *Obstet Gynecol* 2009,**113**:206-217.
31. Hawthorne G. Maternal complications in diabetic pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011,**25**:77-90.
32. Mackay DF, Nelson SM, Haw SJ, Pell JP. Impact of Scotland's smoke-free legislation on pregnancy complications: retrospective cohort study. *PLoS Med* 2012,**9**:e1001175.
33. Haberg SE, Bentdal YE, London SJ, Kvaerner KJ, Nystad W, Nafstad P. Prenatal and postnatal parental smoking and acute otitis media in early childhood. *Acta Paediatr* 2010,**99**:99-105.
34. Pallant J. Statistical technique to explore relationships among variables. In: *SPSS survival manual*. 3 ed; 2007. pp. 126-141.
35. Davison JM. Edema in pregnancy. *Kidney Int Suppl* 1997,**59**:S90-96.
36. Reynolds D. Severe gestational edema. *Journal of Midwifery & Women's Health* 2003,**48**:146-148.
37. Cho S, Atwood JE. Peripheral edema. *Am J Med* 2002,**113**:580-586.
38. Finkler NJ, Safon LE, Ryan KJ. Bilateral postpartum vulvar edema associated with maternal death. *Am J Obstet Gynecol* 1987,**156**:1188-1189.
39. Wang Y, Zhang Y, Zhang J, Tang X, Qian Y, Gao P, et al. Association of a functional single-nucleotide polymorphism in the ALDH2 gene with essential hypertension depends on drinking behavior in a Chinese Han population. *J Hum Hypertens* 2012.
40. Sarkola T, Gissler M, Kahila H, Autti-Ramo I, Halmesmaki E. Alcohol and substance abuse identified during pregnancy: maternal morbidity, child morbidity and welfare interventions. *Acta Paediatr* 2012.
41. Kim SJ, Kim DJ. Alcoholism and diabetes mellitus. *Diabetes Metab J* 2012,**36**:108-115.
42. Hannigan JH, Armant DR. Alcohol in pregnancy and neonatal outcome. *Seminars in Neonatology* 2000,**5**:243-254.
43. Engeland A, Bjorge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol* 2011,**26**:157-163.
44. Ellen R, Wertheimer VNJ. Complications and care Related to Pregnancy, Labor and Delivery, Active component, U:S Armed Forces,2001-2010. In: *Medical Surveillance Monthly Report* Edited by ODonnell FL; 2011. pp. 2-5.
45. Delzell JE, Jr., Lefevre ML. Urinary tract infections during pregnancy. *Am Fam Physician* 2000,**61**:713-721.
46. Meher Rizvi FK, Indu Shukla, Abida Malik, and Shaheen. Rising Prevalence of Antimicrobial Resistance in Urinary Tract Infections During Pregnancy: Necessity for Exploring Newer Treatment Options. *Journal of Laboratory Physicians* 2011,**3**:98-103.

47. Gibbs RS. Premature rupture of the membranes. In: *Danforth's Obstetrics and Gynecology*. Edited by Gibbs RS. 10 ed; 2008. pp. 186-197.
48. Charles R.B. Beckmann FWL, Barbara M. Barzansky, William N.P. Herbert, Douglas W. Laube, Roger P. Smith. Premature Rupture of Membranes. In: *Obstetrics and gynecology*. Edited by Gynecologists TACoOa. 6 ed: Lippincott Williams & Wilkins,a wolters Kluwer business; 2010. pp. 213-217.
49. Neilson JP, Lavender T, Quenby S, Wray S. Obstructed labour. *Br Med Bull* 2003,**67**:191-204.
50. Bergstrom A, Fransson B, Lagerstedt AS, Kindahl H, Olsson U, Olsson K. Hormonal concentrations in bitches with primary uterine inertia. *Theriogenology* 2010,**73**:1068-1075.
51. Zhang J, Bricker L, Wray S, Quenby S. Poor uterine contractility in obese women. *BJOG* 2007,**114**:343-348.