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Cluster Analysis as a Prediction Tool for Pregnancy Outcomes

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ABSTRACT

Considering specific physiology changes during gestation and thinking of pregnancy as a »critical window«, classification of pregnant women at early pregnancy can be considered as crucial. The paper demonstrates the use of a method based on an approach from intelligent data mining, cluster analysis. Cluster analysis method is a statistical method which makes possible to group individuals based on sets of identifying variables. The method was chosen in order to determine possibility for classification of pregnant women at early pregnancy to analyze unknown correlations between different variables so that the certain outcomes could be predicted. 222 pregnant women from two general obstetric offices' were recruited. The main orient was set on characteristics of these pregnant women: their age, pre-pregnancy body mass index (BMI) and haemoglobin value. Cluster analysis gained a 94.1% classification accuracy rate with three branches or groups of pregnant women showing statistically significant correlations with pregnancy outcomes. The results are showing that pregnant women both of older age and higher pre-pregnancy BMI have a significantly higher incidence of delivering baby of higher birth weight but they gain significantly less weight during pregnancy. Their babies are also longer, and these women have significantly higher probability for complications during pregnancy (gestosis) and higher probability of induced or caesarean delivery. We can conclude that the cluster analysis method can appropriately classify pregnant women at early pregnancy to predict certain outcomes.

Key words: *pregnant women, cluster analysis, pre-pregnancy BMI, maternal age, pregnancy outcomes, caesarean delivery, gestosis, weight gain, birth weight, classification.*

Introduction

Pregnancy is a very delicate period in every woman's life when they are more willing to change their lifestyle as well as dietary habits for better[1]. Still, several characteristics of a woman prior pregnancy or in early pregnancy are related to pregnancy outcomes and pregnancy can be considered as a critical window in child's growth and development[2].

One of these important characteristics is woman's age. Women of advanced (35 years) and high (40 years) maternal age do incur a significantly increased risk of obstetric complications and interventions, an increase in type II diabetes and hypertension, maternal mortality, as well as adverse impact on gestational age and birth weight of a child[3,4].

Another important factor is pre-pregnancy weight (expressed as body mass index – BMI). Obesity and overweight have been associated with increased risk of foetal macrosomia and medical complications, including pregnancy-induced hypertension, gestational diabetes, and caesarean delivery[5–9] and nowadays pre-pregnancy obesity is considered as one of the most common high-risk obstetric situations[7,8].

Maternal iron stores are especially important in maintaining homeostasis of iron for the normal growth and development of foetus during pregnancy, presenting itself as a very important factor in foetal programming[2,10]. Even though physiologic anaemia in late pregnancy can be expected, anaemia at early pregnancy should be detected and treated to prevent any of the risks related to pregnancy outcomes, e.g. preterm delivery, small for gestation, low birth weight[11–16].

If we think of complex interaction between women's characteristics prior pregnancy and pregnancy outcomes show complex interactions. Therefore, the analysis that

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would successfully classify women to predict certain outcomes is needed. It would present a tool in foetal programming. Such analysis would recognise and isolate all risk factors to assure the best outcomes for both mother and child.

To test hypothesis above a method emerging from the intelligent data mining was selected; the cluster analysis method. This is a statistical method, based on principles of chaos theory, which emphasizes the search for regularities or patterns and their application in predicting events, classes, or in correlating between different patterns[17]. Cluster analysis seeks to identify homogeneous groups of cases or individuals, in this case pregnant women, where the optimal number of groups, the properties of segments and group membership are unknown in advance. This means that a cluster analysis is used as exploratory technique[18].

The aim of this paper is to illustrate the use of cluster analysis for the classification of pregnant women at early pregnancy in order to predict certain pregnancy outcomes.

Subjects and Methods

Data used for clustering were collected by combining short questionnaire, anthropometric measurements and blood analysis of 222 pregnant women at the beginning of the 1st trimester.

The study was approved by the Ethical committee of Faculty of Food Technology Osijek, and an informed consent was obtained for all participating pregnant women.

Basic data regarding age, education level, incomes and smoking habits of pregnant women at the beginning of the 1st trimester were collected with short questionnaire. Medical scale (Seca, UK) was used for the weight measurement (with the precision of ±0.1 kg), and height measurement (with head in Frankfurt position with the precision of ±0.1 cm). BMI was calculated for all women and it was considered as pre-pregnancy BMI. WHO criteria[19] was considered for the classification of women as underweight (BMI<19.0), normal weighted (BMI ranging from 19.0 to 24.9), overweight (BMI ranging from 25.0 to 29.9) or obese (BMI from 30.0 and more). When the pregnancy was confirmed (by the 12th week of gestation) blood samples were collected and analysed in medical-biochemical laboratory for iron status on OLYMPUS AU400, OLYMPUS AU680 and Coulter LH750 Analyzer. Haemoglobin values were used as a determinant of iron status since it is preferred criteria by the WHO. Incidence of disorders of pregnancy, i.e. edemas, gestational diabetes, hypertension and proteinuria was noted, since they are followed by the gynaecologists for their significant influence on pregnancy outcomes. These four disorders are termed as gestosis. Weight gain was followed and after the delivery it was compared to the recommended weight gain during pregnancy[20]. Data regarding delivery included gestation (in weeks), baby's length and weight and delivery modus (spontaneous, induced or caesarean).

All above mentioned collected characteristics were considered for the cluster analysis. Taking into consideration all determinants for the clustering procedure, cluster analysis procedure included following characteristics of pregnant women: pre-pregnancy body mass index (BMI), age and haemoglobin value. These variables were chosen because of the high level of correlation between chosen ones and the rest of variables. Other available variables were e.g. erythrocytes, haematocrit, serum iron, TIBC, or binary variables which cannot be used for the cluster analysis. Hierarchical method with standardization was chosen[18], presented with dendogram[21]. Dendogram, or *tree diagram* visualize the cluster analysis's progress by displaying the distance level at which there was a combination of objects and clusters. By tracking differences between distance levels in previous and next step of algorithm it is possible to define number of clusters[21]. Discriminant analysis was applied on groups and grouping variables in order to evaluate quality of clustering and to identify variables that have significant influence on group membership. For detailed analysis of each identified group external variables were defined regarding variables describing delivery outcome: weight gain during pregnancy, gestation, delivery modus, gestosis, birth weight and length.

Clustering and statistical calculations were done with software tool Statistica 10.0 (StatSoft, Tulsa, OK, USA).

Results

Clusters were defined when examining dendogram (Figure 1) which graphically presents result of the cluster analysis. The biggest step in Ward's algorithm is from 38% to 87% and in that step algorithm should be stopped. This procedure results in three clusters representing three groups of pregnant women.

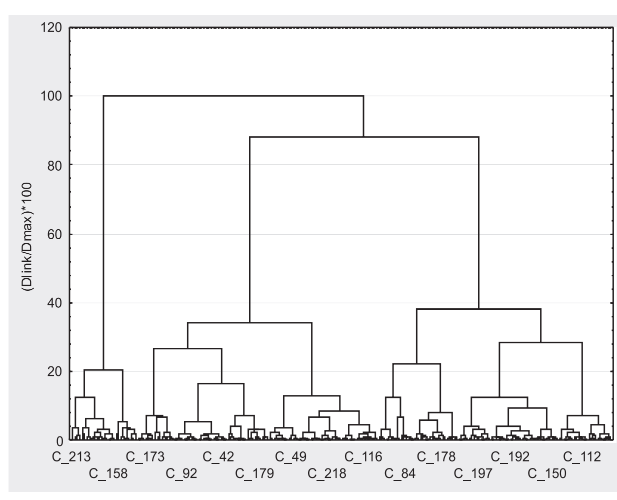

Fig. 1. Dendogram showing clusters after analysis for three variables (age, pre-pregnancy BMI and haemoglobin) for pregnant women (N=222).

TABLE 1
DISTRIBUTION OF VARIABLES INCLUDED IN THE CLUSTER ANALYSIS OF PREGNANT WOMEN (N=222)

Variables		CLUSTER GROUP			p*
		Younger N=96 Median (25%–75%)	Average N=99 Median (25%–75%)	Overweight N=27 Median (25%–75%)	
Variables included in cluster analysis	Age (years)**	25.0 (22.3–27.0)	32.0 (30.0–33.0)	33.0 (31.0–35.0)	<0.001
	Pre-pregnancy BMI (kg/m^2)**	21.9 (20.3–24.3)	21.7 (20.4–24.0)	31.2 (28.2–34.9)	<0.001
	Haemoglobin (g/L)	129 (124–134)	127 (122–133)	126 (123–135)	0.354
External numerical variables	Weight gain (kg)	15.0 (12.5–17.9)	14.5 (12.0–16.5)	12.0 (8.0–15.5)	0.016
	Baby's birth weight (g)	3,500.0 (3,157.5–3,780.0)	3,460.0 (3,100.0–3,690.0)	3,800.0 (3,350.0–4,150.0)	0.010
	Baby's length (cm)	50 (49–51)	50 (49–51)	51 (50–52)	0.261

* Kruskal Wallis Test, ** Variables that have significant influence on group membership

Classification of discriminant analysis showed that a 94.1% of original grouped cases were correctly classified and canonical discriminant functions gave variables that significantly influenced group membership (Table 1).

Distributions of external variables between categorized groups are shown in Tables 1 and 2. First group can be called the »younger« with significant influence of the variable age (p<0.001) third group can be called the »overweight« with significant influence of the variable BMI (p<0.001) while none of the three variables used for clustering significantly influenced on the second group, the »average« pregnant women.

Discussion

Results gained when the cluster analysis statistical method was applied has proven as consistent and of high usage, as they are highly comparable to results gained by other methods used in different studies. Comparisons of gained results with other studies' results are discussed below.

The impact of obesity on pregnancy outcomes has been reviewed numerous times. Pregravid obesity is one of the most common high-risk obstetric situations[7,22]. Even moderate overweight is a risk factor for gestational diabetes

TABLE 2
DISTRIBUTION OF EXTERNAL VARIABLES AMONG THREE CLUSTERS OF PREGNANT WOMEN (N=222)

External variable		Younger N (%)	Average N (%)	Overweight N (%)	p*
Gestosis	Yes	26 (27)	28 (28)	18 (67)	<0.001
	No	70 (73)	71 (72)	9 (33)	
Delivery modus	Spontaneous	69 (72)	65 (66)	11 (41)	0.054
	Caesarean	19 (20)	24 (24)	11 (41)	
	Induced	8 (8)	10 (10)	5 (18)	
Gestation (weeks)	<37th	4 (4)	9 (9)	3 (11)	0.171
	37^{+1} – 40th	57 (59)	56 (57)	18 (67)	
	40^{+1} – 40^{+6}	21 (22)	28 (28)	3 (11)	
	≥41th	14 (15)	6 (6)	3 (11)	

* Fisher Exact Test

and hypertensive disorders of pregnancy, and the risk is higher in subjects with overt obesity. Maternal overweight is related to a higher risk of cesarean deliveries and macrosomia, increases maternal and fetal morbidity. Also, long term complications such as worsening of maternal obesity and development of obesity in the infant can be observed[7].

Clinical review by Duvekot[22] emphasizes the complications obesity has on pregnancy outcomes. Complications include hypertensive disorders, gestational diabetes mellitus, caesarean section, and postpartum and postoperative infections. On the other hand, neonatal consequences include an increased rate of congenital anomalies, stillbirth, and macrosomia[22]. This was also confirmed in a large cohort study published in 2006. by Doherty et al.[23].

A population-based study on pregnant women by Sheiner et al.[24] using a multivariable analysis found a significant association between maternal obesity and incidence of caesarean section. Association existed even after exclusion of obese pregnant women with hypertensive disorder or diabetes mellitus. But still, that they did not found association between obesity alone and adverse perinatal outcome (e.g. perinatal mortality, congenital malformations, shoulder dystocia and low Apgar scores)[24]. A recent study by Roman et al.[25] confirmed significant association between maternal obesity (expressed as increasing BMI) with adverse maternal and neonatal outcomes. Adverse outcomes were more expressed among women with gestational diabetes mellitus[25]. An extensive review by Yogev and Visser is dealing with the combined influence of maternal obesity and gestational diabetes on pregnancy outcomes[26]. Similar adverse impact of overweight and obesity among pregnant women on maternal and neonatal outcomes was confirmed in large population study in Australia[27] and a small study conducted on pregnant women with hyperglycaemia at the University Hospital Rijeka, Croatia[9].

Interestingly, Choi et al.[28] found that inadequate weight gain among normal weight, or underweight pregnant women, was significantly associated with adverse maternal and neonatal outcomes[28].

As maternal weight is a modifiable risk factor with many lifelong health effects and 54% of women of childbearing age are either overweight or obese, more care should be given to that matter. A study of Vahratian et al.[8] support the premise that women who are obese, and to a lesser extent those who are overweight prior to conception, may be at increased risk for a cesarean delivery. They found that women who are overweight prior to pregnancy have a 21% increase in risk for cesarean delivery compared with normal weight women[8].

Age distribution shows that the group of overweight pregnant women has the highest median of 33 years, and a range of 31 to 35 years (Table 1). Maternal age is very important determinant in pregnancy outcomes, especially when speaking of pregnant women in later 30s. Nybo Andresen et al.[29] found that the risk of fetal loss according to maternal age at conception followed a J-shaped curve, with a steep increase after 35 years of age, meaning that one fifth of all pregnancies in 35 year old and even half of pregnancies at 42 year old women results with fetal loss. Miletić et al.[4] found the same adverse trend between pregnancies in women of 40 and over, pregnancy complications, pregnancy outcomes and neonatal outcomes in a large retrograde study from Gynaecology and Obstetrics Clinics from Split and Šibenik. The same trend was established for the spontaneous abortion and stillbirths, for which substantially increased trend for stillbirths was found in teenage pregnancies as for the 35–39 year age group[29]. If the influence of age on pregnancy outcome is observed separately we can expect increased risk in overweight cluster group. Adverse influence of advanced maternal age on pregnancy outcomes was proven by other researches[4,30–32,33], even though the higher maternal age is related to better nutritional habits during pregnancy[1]. It also has to be noted that nowadays women have higher tendency to delay childbearing for social reasons. On the other hand, overweight status among pregnant women is usually related to low socioeconomic status and low education level[1,34], consequently resulting in worse nutritional habits during pregnancy[1]. Still, combination of higher maternal age and higher BMI in the overweight cluster group is expected to results in greater inverse risks for pregnancy outcomes.

Iron stores and iron status before conception and during pregnancy should also be taken into consideration since they are related to woman's age, nutritional habits, and socioeconomic status[1,11,14,35]. The importance of iron stores and status are emphasized for their adverse impact on pregnancy outcomes, e.g. preterm delivery, fetal growth restriction, low birth weight[11,14]. WHO criterion for iron deficiency (anaemia) in pregnant women is haemoglobin (Hgb) level of 110 g/L or below[19]. Higher body weight is related to a better iron status, especially in terms of iron stores[11,36–38]. Even though Hgb levels at the 1st trimester of pregnancy used as one of entering variables for the cluster analysis do not show statistically significant difference between three cluster groups, still the overweight group shows the lowest Hgb median of 126 g/L (Table 1). Iron stores of young women are expected to be low, especially if they are also of low socioeconomic status[11,37], but the clustering analysis shows that the younger group has the best iron status with median Hgb of 129 g/L (Table 1). The lack of correlation for Hgb status between these three cluster groups can be explained by relatively high age median of 25 years for the younger group (Table 1). It is important that we emphasize that although Hgb level during pregnancy, as a parameter of iron deficiency (anaemia) can be analyzed in terms of its impact on pregnancy outcomes, here was tested only the difference in Hgb value between three cluster groups, and not its influence on delivery outcome.

Pregnancy outcomes in terms of newborn have shown the highest birth weight (3800 g, $p=0.010$) and length (51 cm) among the overweight group (Table 1). Numerous researches have proven the relation between high birth weight infants, macrosomic infants and overweight and/

or obese condition in mother[5,6,8,22,25,26,28,34,39]. Even though difference in length is not statistically significant, trend in higher baby's length among the overweight group is obvious, ranging from 50 to 52 cm (Table 1). That is somehow expected since infants of mother's from the overweight group are also the heaviest.

Weight gain during pregnancy, as well as woman's pre-pregnancy BMI are very important in terms of developing pregnancy disorders (i.e. gestosis), such as hypertensive disorders in pregnancy or gestational diabetes[9,33,39]. Choi et al.[28] found that even in pregnant women who started pregnancy with normal pre-pregnancy BMI or as underweigh, excessive weight gain during pregnancy results in significantly increased neonatal and maternal complications. Weight gain was used as one of external variables in the cluster analysis procedure, and it shows statistically significant difference between three cluster groups of $p=0.016$ (Table 1). The group of younger has the highest weight gain of 15.0 kg/gestation, and the lowest weight gain of 12.0 kg/gestation was observed among overweight group (Table 1).

In terms of disorders of pregnancy (i.e. gestosis), which were observed as another external variable for their adverse impact on pregnancy outcomes[33,40,41], statistically significant difference was found between three cluster groups ($p<0.001$; Table 2). As proven by so many researches[6,9,24–26,34], the highest incidence of gestosis was found in the overweight group (67%; Table 2). The average cluster group of pregnant women, as well as the younger group did not differ significantly (28% in the *average* or 27% in the younger; Table 2).

Delivery modus or pregnancy duration do not show any statistical difference between three cluster groups (Table 2). On the other hand, trend of higher incidence of spontaneous delivery among the younger group is visible (72%, unlike 66% in the average or 41% in the overweight), as well as the trend of higher incidence of caesarean (41% unlike 24% in the average or 20% in the younger) and induced (18%, vs 10% in the average or 8% in the younger) delivery in the overweight group (Table 2). The same trend in the increased risk for caesarean delivery among overweight and obese pregnant women was confirmed by Vahratiana et al.[8], although the risk was a bit smaller than previously reported by Baeten et al.[5]. On the other hand, a large population study from Finland confirmed that overweight condition increases obstetric risks in BMI-dependent manner, with increased risk of induced and caesarean delivery among overweight and obese women[6]. Therefore, the observed trends were expected.

Obese and overweight pregnant women are at elevated risk for delivering prematurely. Baeten et al.[5] showed that obese and overweight pregnant women were at increased risk for delivering at or before 32 weeks' gestation and were slightly more likely to deliver before 37 weeks. Another factor influencing pregnancy duration is presence of iron deficiency (anaemia), which can be expressed at any trimester[11,14]. Pregnancy duration also shows some expected trends (Table 2). Higher incidence of delivery before 37th was found in the overweight (11%) and for the delivery after 41st week of gestation in the younger group (15%). Observed trend in the younger group is expected since results point out that this group had the highest weight gain (Table 1).

Conclusions

Cluster analysis at the 1st trimester of pregnancy (by variables age, pre-pregnancy BMI and haemoglobin) gave three extremely different groups of pregnant women. Comparison of distributions of variables describing gestation and pregnancy outcome gave significant results for weight gain, birth weight and complications during pregnancy and for delivery modus at the level of significance. Still, for other variables (baby's length, delivery modus and gestation) trends of correlation can be observed.

The results are showing that pregnant women both of older age and higher pre-pregnancy BMI have a significantly higher incidence of delivering baby of higher birth weight but they gain significantly less weight during pregnancy. Their babies are also longer, and these women have significantly higher probability for complication during pregnancy (gestosis) and higher probability of induced or caesarean delivery.

Cluster analysis is a useful method in predicting and grouping pregnant women at early pregnancy, and can be used for the prevention of certain risk factors during pregnancy.

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KLASTER ANALIZA KAO PREDIKCIJSKI ALAT ZA ISHOD TRUDNOĆE

S A Ž E T A K

Uzimajući u obzir specifične fiziološke promjene tijekom gestacije i ako o trudnoći razmišljamo kao o »kritičnom prozoru«, klasifikacija trudnica u ranoj trudnoći može se smatrati ključnom. Rad ilustrira uporabu metode koja se bazira na pristupu iz inteligentne obrade podataka, klaster analize. Metoda klasteriranja je statistička metoda koja omogućuje grupiranje individua na osnovi seta identificirajućih varijabli. Metoda je odabrana kako bi se odredila mogućnost klasifikacije trudnica u ranoj trudnoći analiziranjem nepoznatih korelacija između različitih varijabli kako bi se predvidjeli određeni ishodi. Regrutirano je 222 trudnice iz dvije ginekološke ordinacije. Glavna je orjentacija bila usmjerena na karakteristike ovih trudnica: njihova dob, predtrudnički indeks tjelesne mase (BMI) i vrijednost hemoglobina. Klaster analiza je dala 94,1%-tnu točnost klasifikacije s tri grane ili skupine trudnica koje su pokazale statistički značajne korelacije s ishodima trudnoće i/ili poroda. Rezultati pokazuju kako starije trudnice višeg predtrudničkog BMI imaju značajno višu incidenciju poroda djeteta veće porođajne mase, ali tijekom trudnoće dobiju značajno manje kilograma. Njihova su novorođenčad dulja i ove žene imaju značajno veću vjerojatnost za komplikacije tijekom trudnoće (gestoze) i veću vjerojatnost induciranog ili poroda carskim rezom. Možemo zaključiti kako metoda klaster analize može adekvatno klasificirati trudnice u ranoj trudnoći kako bi se predvidjeli određeni ishodi.