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Adverse obstetric and neonatal outcomes of pregnancy in high-risk women with heart disease

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Background: The latest ESC guidelines on the management of cardiovascular diseases during pregnancy recommend estimating maternal cardiovascular risk according to the modified World Health Organization (mWHO) classification. In contrast, there are no validated models for predicting neonatal and obstetric risk in these women.
Objectives: To compare the neonatal and obstetric outcomes of pregnancy between two groups of mothers with heart disease: women at high to extremely high maternal risk (mWHO III-IV; group 1) and women at low to intermediate maternal risk (mWHO < III; group 2).
Methods: We included 48 consecutive women with clinically significant congenital heart diseases, valvular diseases, cardiomyopathies, aortic diseases, or heart rhythm disorders in a retrospective study. We assessed pregnancy outcomes in group 1 (19 pregnancies in 17 women, with 20 live-born neonates) and in group 2 (35 pregnancies in 31 women, with 34 live-born neonates).
Results: In group 1, there was a higher prevalence of newborns with low birth weight (50.0% vs 2.9%, $p < 0.001$), a lower prevalence of mature newborns (50.0% vs 94.1%, $p < 0.01$) and higher prevalence of preterm delivery (45.0% vs 5.9%, $p < 0.01$). Newborns of group 1 mothers had a significantly lower birth weight (2442±753 g vs 3285±457 g, $p < 0.0001$). Patients in group 1 gave birth significantly earlier than in group 2 (35.7±3.1 weeks vs 38.5±1.3 weeks, $p < 0.00001$). They had longer hospital stay (13.0±14.0 days vs 5.0±2.3 days, $p < 0.001$), higher prevalence of deliveries per Caesarean section (100% vs 63.6%, $p < 0.01$), and higher estimated blood loss during operative delivery (572±156 ml vs 474±111 ml, $p < 0.05$). We found a significantly higher risk of neonatal and obstetric complications of pregnancies in mWHO III-IV classes vs pregnancies in mWHO < III classes: delivery per Caesarean section (odds ratio [OR] 22.7, 95% confidence interval [CI] 1.3-409.0, $p < 0.05$), preterm delivery (OR 13.1, 95% CI 2.4-70.1, $p < 0.01$), low birth weight (OR 33.0, 95% CI 3.8-290.2, $p < 0.01$), neonatal immaturity (OR 16.0, 95% CI 3.0-85.5, $p < 0.01$).
Conclusion: Pregnancy in women at high to extremely high maternal risk (mWHO III-IV) was burdened with a high risk of neonatal and obstetric complications. We found significantly worse obstetric and neonatal outcomes in pregnancies in mWHO classes III-IV than in mWHO classes < III.

Key words: heart disease, mWHO classification, neonatal outcomes, obstetric outcomes, pregnancy.

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Nepriaznivé pôrodnícke a novorodenecké výsledky gravidít u vysoko rizikových žien s ochorením srdca

Východisko: Aktuálne guidelines Európskej kardiologickej spoločnosti pre manažment ochorení srdca v gravidite odporúčajú na hodnotenie maternálneho kardiovaskulárneho rizika modifikovanú klasifikáciu World Health Organization (mWHO). Naproti tomu neexistujú validované modely na predikciu novorodeneckého a pôrodníckeho rizika u týchto žien.

Ciele: Porovnať novorodenecké a pôrodnícke výsledky gravidít medzi dvoma skupinami matiek s ochorením srdca: ženy s vysokým až extrémne vysokým maternálnym rizikom (mWHO III-IV; skupina 1) a ženy s nízkym až intermediárnym maternálnym rizikom (mWHO < III; skupina 2).

Metodika: Zaradili sme 48 následných žien s klinicky významnými vrodenými chybami srdca, chlopňovými chybami, kardiomyopatiami, ochoreniami aorty alebo poruchami rytmu. Hodnotili sme výsledky gravidity v skupine 1 (19 gravidít u 17 žien, 20 živorodených novorodencov) a v skupine 2 (35 gravidít u 31 žien, 34 živorodených novorodencov).

Výsledky: V skupine 1 bola vyššia prevalencia novorodencov s nízkou pôrodnou hmotnosťou (50.0% vs 2.9%, p < 0.001), nižšia prevalencia zrelých novorodencov (50.0% vs 94.1%, p < 0.01) a vyššia prevalencia predčasného pôrodu (45.0% vs 5.9%, p < 0.01). Novorodenci matiek skupiny 1 mali signifikantne nižšiu pôrodnú hmotnosť (2442±753 g vs 3285±457 g, p < 0.0001). Pacientky skupiny 1 mali významne skorší pôrod ako v skupine 2 (35.7±3.1 týždňov vs 38.5±1.3 týždňov, p < 0.00001). Mali dlhšiu dobu hospitalizácie (13.0±14.0 dní vs 5.0±2.3 dní, p < 0.001), vyššiu prevalenciu pôrodov cisárskym rezom (100% vs 63.6%, p < 0.01) a vyššie odhadované krvné straty pri operačnom pôrode (572±156 ml vs 474±111 ml, p < 0.05). Zistili sme signifikantne vyššie riziko novorodeneckých a pôrodníckych komplikácií pri graviditách v triedach mWHO III-IV ako pri graviditách v triedach mWHO < III: pôrod cisárskym rezom (odds ratio [OR] 22.7, 95% konfidenčný interval [CI] 1.3-409.0, p < 0.05), predčasný pôrod (OR 13.1, 95% CI 2.4-70.1, p < 0.01), nízka pôrodná hmotnosť (OR 33.0, 95% CI 3.8-290.2, p < 0.01), nezrelosť novorodenca (OR 16.0, 95% CI 3.0-85.5, p < 0.01).

Závery: Gravidita u žien s vysokým až extrémne vysokým maternálnym rizikom (mWHO III-IV) bola zaťažená vysokým rizikom novorodeneckých a pôrodníckych komplikácií. Zistili sme signifikantne horšie pôrodnícke a novorodenecké výsledky u gravidít v triedach mWHO III-IV ako v triedach mWHO < III.

Kľúčové slová: gravidita, klasifikácia mWHO, novorodenecké výsledky, ochorenie srdca, pôrodnícke výsledky.

The latest ESC guidelines on the management of cardiovascular diseases during pregnancy recommend estimating maternal cardiovascular risk according to the modified World Health Organization (mWHO) classification (1). Though predictors of offspring complications have been identified, there are no validated models for predicting neonatal and obstetric risk.

Methods

This is a non-interventional observational retrospective monocentric study. We included consecutive women with a history of clinically significant heart disease who gave birth between January 2011 and May 2022. A total of 48 women with congenital heart diseases, valvular heart diseases, cardiomyopathies, aortic diseases, or heart rhythm disorders were recruited. We did not include patients with arterial hypertension, venous thromboembolism, or patients with mild and clinically insignificant heart diseases as judged by the investigators if they did not have the aforementioned heart disease. There were no other exclusion criteria used for inclusion in the study.

Patients were classified into maternal risk classes according to the mWHO classification (1). These were classes mWHO I, mWHO II, mWHO II-III, mWHO III, and mWHO IV. If it was not possible to exactly classify the mother and she did not meet any of the mWHO III or IV criteria, we classified her as mWHO < III.

We aimed to compare the neonatal, obstetric, and maternal outcomes of pregnancy between two groups of mothers with heart disease: group 1 with significant to extremely high risk (mWHO III, mWHO IV) and group 2 with low to intermediate risk (mWHO I, mWHO II, mWHO II-III, mWHO < III). There were 17 mothers in group 1 and 31 mothers in group 2.

Preterm delivery was defined as birth before the end of the 37th week of gestational age. We considered low birth weight to be < 2500 g. We evaluated neonatal mortality during the first 28 completed days of life. Fenton growth charts were used to assess growth.

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous data are presented as mean and standard deviation if normally distributed and median with interquartile range if not normally distributed. The normality of the distribution of continuous variables was tested with the Kolmogorov-Smirnov test of normality. The frequencies of categorical data were compared by Pearson's chi-square test. The Fisher exact test was employed when sample sizes were small. The differences in mean values of continuous variables were evaluated using a T-test in the case of a normal distribution. In the absence of a normal distribution, we compared the difference in the means of continuous variables using the Mann-Whitney U test. We considered the differences to be statistically significant at a significance level of p < 0. 05. All statistical calculations were carried out using SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20. 0. Armonk, NY: IBM Corp.).

Tab. 1a. *Leading cardiovascular diagnosis in patients of group 1 (mWHO III-IV)*

	mWHO class	n
Pulmonary arterial hypertension	IV	3
Severe systolic dysfunction of the systemic ventricle[1]	IV	3
Asymptomatic severe aortic stenosis	III	3
Mechanical valvular prosthesis, oral anticoagulation	III	2
Status after ICD implantation for secondary prevention[2]	III	2
Moderate systolic dysfunction of the left ventricle	III	2
Fontan circulation without complications	III	1
Aortic aneurysm, severe asymptomatic aortic regurgitation	III	1

[1] – 1× dilated cardiomyopathy, 1× severe mitral regurgitation with pulmonary edema,1× status after Senning operation for uncorrected transposition of the great arteries with global dysfunction of the systemic right ventricle; [2] – 1× pulseless ventricular tachycardia and ventricular fibrillation,1× polymorphic ventricular tachycardia (both patients after cardiopulmonary resuscitation)

Tab. 1b. *Leading cardiovascular diagnosis in patients of group 2 (mWHO < III)*

	mWHO class	n
Congenital heart diseases	II-III[1] < III II I	4 3 1 6
Asymptomatic moderate aortic stenosis	II-III	3
Hypertrophic obstructive cardiomyopathy[5]	II-III	1
Severe aortic regurgitation	II-III	1
Loeys-Dietz syndrome without aortic dilatation	II-III	1
Third-degree atrioventricular block	< III	4
Status after heart transplantation[2]	< III	1
Left ventricular pseudoaneurysm[3]	< III	1
Incessant nonsustained ventricular tachycardia[4]	< III	1
Symptomatic ventricular preexcitation	II	3
Atrioventricular nodal reentry tachycardia[6]	II	1

[1] – 3× status after surgery for tetralogy of Fallot with severe residual pulmonary regurgitation, 1× hemodynamically severe partial anomalous pulmonary venous return; [2] – for heart failure due to hypertrophic cardiomyopathy; [3] – after mitral valvuloplasty for infective endocarditis; [4] – status after radiofrequency catheter ablation of the substrate; [5] – status after septal myectomy and mitral valvuloplasty; [6] – with extreme tachycardia

Results

In group 1, we analyzed 19 pregnancies in 17 women, with 20 fetuses and 20 live-born neonates. In group 2, there were 35 pregnancies in 31 women, with 36 fetuses and 34 live-born neonates, while two pregnancies ended in miscarriages.

The most common heart diseases were congenital heart diseases (33.3% of the total cohort), heart rhythm disorders (22.9%), and valvular heart diseases (20.8%). This was followed by pulmonary arterial hypertension (6.3%), cardiomyopathies (4.2%), and aortic diseases (4.2%).

An overview of cardiac diagnoses in groups 1 and 2 are presented in Table 1a and 1 b, respectively. Six patients (12.5% of the total cohort) had an extremely high risk of maternal mortality or severe morbidity (mWHO IV). Eleven patients (22.9%) had a significantly increased risk of maternal mortality or severe morbidity (mWHO III). The remaining 31 patients (64.6%) had low to intermediate risk. In group 1, two patients were on full anticoagulation therapy (both for mechanical valve prostheses; 11.8% of the patients). In group 2 there was no patient on anticoagulation therapy.

The characteristics of both groups are shown in Table 2. The groups did not differ significantly in average age, the percentage of twin pregnancies, primipara, or in the number of abortions in previous pregnancies.

Tab. 2 *Characteristics of pregnancies*

	Group 1 (n = 19)	Group 2 (n = 35)	p
Age (years)	31.9 ± 3.7	30.3 ± 4.7	NS
Twin pregnancies	1 (5.3%)	1 (2.9%)	NS
Primipara	11 (57.9%)	23 (65.7%)	NS
Prior abortion	7 (36.8%)	6 (17.1%)	NS

NS – not significant

The obstetric outcomes are presented in Table 3. In several aspects, they were significantly worse in group 1. High-risk women gave birth significantly earlier than low-risk women. They had a significantly longer hospitalization, a higher proportion of deliveries per Caesarean section (C.s.), and higher estimated blood loss during operative delivery. All patients in group 1 underwent operative delivery. Operative vaginal delivery using vacuum extraction was performed only in group 2 (9.4% of all deliveries). Emergent operative delivery was not indicated for any parturient. Intra-amniotic infection was not detected in any case.

The most significant differences between groups were related to neonatal outcomes (Table 4). Newborns of mWHO class III and IV mothers had significantly lower birth weight and length and worse Apgar scores (one minute and five minutes). In group 1, there was

Tab. 3. *Obstetric outcomes of pregnancies*

	Group 1 (n = 19)	Group 2 (n = 33*)	p
Length of hospitalization (days; median ± IQR)	13.0 ± 14.0	5.0 ± 2.3	< 0.001
Birth per Caesarean section	19 (100%)	21 (63.6%)	< 0.01
Completed week of pregnancy	35.7 ± 3.1	38.5 ± 1.3	< 0.0001
Estimated blood loss (ml)	572 ± 156	474 ± 111	< 0.05
Oligohydramnion	1 (5.3%)	1 (3.0%)	NS
Preeclampsia	1 (5.3%)	0 (0%)	NS

*IQR – interquartile range, NS – not significant, * – calculation in Group 2 from the number of 31 pregnancies (two pregnancies that terminated in abortions were excluded from the evaluation)*

Tab. 4. *Neonatal outcomes of live-born newborns*

	Group 1 (n = 20)	Group 2 (n = 34)	p
Neonatal mortality	0 (0%)	0 (0%)	NS
Birth weight (g)	2442 ± 753	3285 ± 457	< 0.00001
Newborn length (cm)	45.8 ± 4.6	49.8 ± 1.5	< 0.0001
Apgar score (one-minute)	7.3 ± 2.1	9.1 ± 1.0	< 0.001
Apgar score (five-minutes)	8.6 ± 1.4	9.7 ± 0.6	< 0.001
Preterm delivery	9 (45.0%)	2 (5.9%)	< 0.01
Low birth weight	10 (50.0%)	1 (2.9%)	< 0.001
Mature newborn	10 (50.0%)	32 (94.1%)	< 0.01

NS – not significant

Tab. 5. *Maternal outcomes of pregnancies*

	Group 1 (n = 19)	Group 2 (n = 35)	p
Maternal mortality	1 (5.3%)	0 (0%)	NS
Heart failure	4 (21.1%)	1 (2.9%)	< 0.05
Supraventricular tachycardia	0 (0%)	1 (2.9%)	NS
Ventricular tachycardia	1 (5.3%)	1 (2.9%)	NS

NS – not significant

a significantly higher prevalence of newborns with low birth weight and, conversely, a significantly lower prevalence of mature newborns. These mothers had a significantly higher risk of preterm delivery. In group 1, nine out of 19 newborns were premature, of which three were very premature (gestational weeks 28-31) and six moderately premature (gestational weeks 32-36). In group 2, there were two moderately premature births out of 34 live-born fetuses. Not a single newborn in this group was very premature. No neonatal mortality occurred in either group. In group 2, the frequency of abortions was insignificantly higher than in group 1 (5.6% vs 0% of fetuses).

We found no significant differences between groups regarding maternal outcomes except for increased prevalence of heart failure in group 1 (Table 5). Among all pregnant women, one patient died (mWHO IV), which corresponded to maternal mortality of 1.9% of all pregnancies. This was a 31-year-old primigravida with severe pulmonary arterial hypertension (PAH), which was diagnosed in the 35th week of pregnancy. None of the pregnant women had a thrombotic event, aortic dissection during pregnancy or up to discharge, or postpartum haemorrhage.

Odds ratios (OR) of selected obstetric and neonatal outcomes of pregnancies are given in Figure 1.

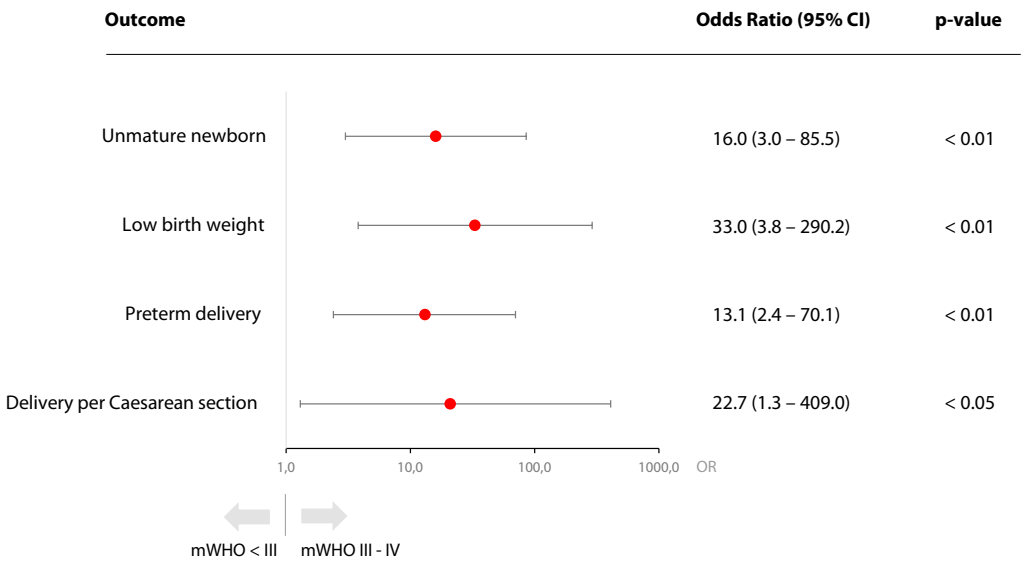
Discussion

Obstetric and offspring risks are increased in women with heart disease. The magnitude of them is related to maternal cardiac risk (2). In the current study group, we found significantly worse obstetric and neonatal outcomes in mWHO III-IV classes compared to mWHO < III classes. The most robust data on pregnancy outcomes in women with heart diseases is provided by the ROPAC registry (3). In the years 2007-2018, 5739 pregnancies were prospectively included in 138 centers in 53 countries. Congenital heart diseases (57%) and valvular diseases (29%) dominated. Maternal mortality was 0.6%, while the highest was in PAH – 9% (3). This corresponds to our experience when the only maternal death was in a pregnant woman with PAH (maternal mortality 1,9%).

Obstetric complications were very common in the ROPAC registry – 17% (3). It also corresponds to our results, especially in mWHO classes III-IV. All our patients in these classes had an operative delivery and, compared to lower-risk patients in mWHO classes < III, they had a significantly shorter duration of pregnancy, longer hospitalization, and greater blood loss.

Special attention should be paid to the termination of pregnancy per C.s. According to the ESC, the indications are limited – dilatation of the ascending aorta > 45 mm, severe aortic stenosis, severe pulmonary hypertension (including Eisenmenger syndrome), severe heart failure, and prenatal treatment with oral anticoagulants (recommendation class IIa, level of evidence C) (1). In the ROPAC registry, the pregnancy was terminated per C.s. in 44% of pregnancies (3). In our cohort, deliveries per C.s. were more often and over-indicated, compared to ESC guidelines and the ROPAC registry. The prevalence of deliveries per C.s. was 100% in mWHO classes III-IV, 64% in mWHO classes < III, and 77% in our total cohort. Indication criteria for the delivery per C.s. were met according to the ESC guidelines in the given groups only in 79%, 0% (!), or 29% of

Fig. 1. *Odds ratios (OR) of selected obstetric and neonatal outcomes of pregnancies*



the deliveries. At the same time, all indications for the delivery per C.s. were declared as cardiac. The striking discrepancy in mWHO < III classes (64% vs 0%) probably reflects the concern of the attending physicians that these patients are also too risky and that operative delivery is the best solution. According to the ESC guidelines, planned delivery per C.s. in them has no maternal benefit and leads to earlier termination of pregnancy and lower birth weight (1), which fully corresponds to our results. An unfavorable phenomenon in Slovakia is steadily increasing trend to terminate pregnancy in women with heart disease per C.s.

When comparing the classes mWHO III-IV and mWHO < III, we found the most pronounced differences in **neonatal complications**. Newborns of mothers with high to extremely high risk had a significantly lower birth weight. The prevalence of newborns with low birth weight as well as the prevalence of preterm deliveries were significantly higher. We observed worse results in these parameters than in the ROPAC registry (3). The prevalence of low birth weight and preterm deliveries was equally 20.4% in our total cohort (vs 11.7% and 15.8% in ROPAC, respectively). In the ROPAC registry, congenital heart disease (CHD) was associated with spontaneous preterm birth (OR [odds ratio] = 1.8, 95% CI [confidence interval] = 1.2-2.7). Complex CHD was associated with small-for-gestational-age neonates (OR = 2.3, 95% CI = 1.5-3.5). Jastrow et al. reported preterm delivery in 16.7% of 312 pregnancies in women with heart disease (4). Toprak et al. found an identical finding as in our group – a significantly higher prevalence of preterm deliveries in women with CHD and mWHO classes III-IV than in mWHO classes I-II (5). Also in the Mexican group (399 births) the association between mWHO class and preterm deliveries was confirmed (6). Suwanrath et al. analysed 331 cases of pregnant women with heart disease. Adverse fetal outcomes including preterm delivery, low birth weight, small for gestational age and neonatal intensive care unit admission were significantly increased in mWHO classes III and IV. They concluded that the mWHO classification is useful not only for obtaining a cardiovascular risk assessment in pregnant women with heart disease but also for predicting adverse fetal outcomes (7).

Neonatal mortality did not occur in our cohort. In the ROPAC registry, foetal mortality occurred in 1.7% and neonatal mortality in 0.6%, both higher than in the normal population (8). Italian authors reported the single-center experience in 51 pregnancies of women with cardiovascular disease. There was no neonatal mortality, just like in our study group (9).

The proportion of extremely high-risk pregnancies in the mWHO class IV is generally increasing. It was only 0.7% in the ROPAC registry in the years 2007-2010, but already 10.9% in the years 2015-2018 (3). Analogously, in our group (years 2011-2022), 12.5% of pregnant women were in mWHO class IV. These mothers have an extremely high risk of maternal mortality or severe morbidity (40-100%). According to the ESC guidelines, pregnancy is contraindicated for them, and if it occurs, its termination should be considered (1). Even for women in mWHO class III, the risk is high: 19-27% (1). Nevertheless, in our experience, most pregnancies in mWHO classes III-IV were intentional and not accidental.

According to the ESC guidelines all women in mWHO classes III-IV should be monitored throughout the pregnancy in expert centers for pregnancy and cardiac disease. The deliveries are also to be carried out in these centers (1). Significantly worse obstetric and neonatal outcomes in mWHO III-IV classes found in our study are in accordance with this statement. For pregnant women with cardiac diseases in mWHO classes < III, follow-up and delivery can be performed in local or referral hospitals (1).

The mWHO classification is designed to predict maternal risk. van Hagen et al. evaluated the potential of the mWHO classification for the prediction of obstetric and fetal complications in women with structural heart disease. There were 2742 pregnancies. The mWHO classification performed poorly in predicting obstetric (c-statistic = 0.60) and fetal events (c-statistic = 0.56) (10).

Several risk scores are used to stratify the risk of cardiac complications of pregnancy in women with heart disease. The mWHO, CARPREG, and ZAHARA systems are most often reported in the literature (11-13). Balci et al. prospectively validated cardiovascular and offspring risk models for pregnant women with CHD. They determined the outcomes of 213 pregnancies in 203 women. The ZAHARA I, CARPREG, and mWHO models were evaluated. Offspring events occurred during 77 pregnancies in 81 children (37.3%). All models performed insufficiently in predicting offspring events (AUC [area under the curve] ≤ 0.6) (14).

Limitations

A limitation of the study is the retrospective design and small sample size. We did not include patients with clinically insignificant heart disease. Therefore, there may be a certain form of selection bias. Risk categorization according to mWHO classes does not allow for accurately classifying all pregnant women with heart disease. That is why we created the mWHO < III class. Since these parturients did not exactly meet the criteria of mWHO classes III or IV, we do not assume that their inclusion in group 1 significantly affected the results.

Conclusions

Pregnancy in women at high to extremely high maternal risk (mWHO III-IV) was burdened with a high risk of neonatal and obstetric complications. We found significantly worse obstetric and neonatal outcomes in pregnancies in mWHO classes III-IV than in mWHO classes < III.

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