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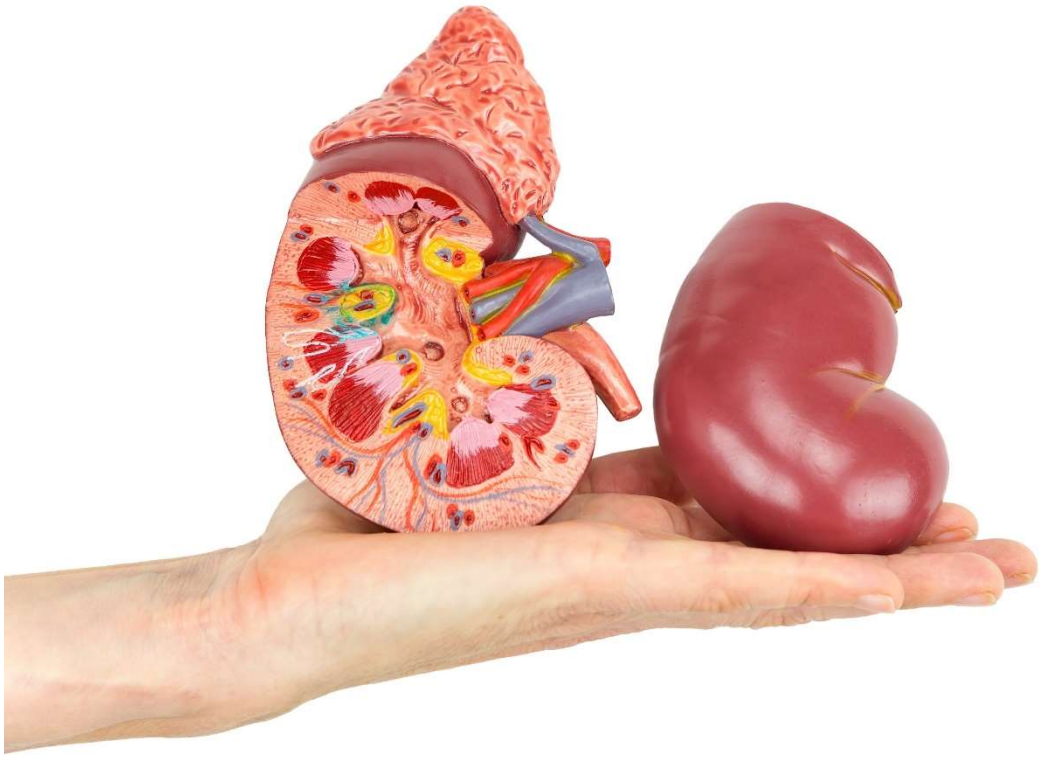

THE INITIAL FUNCTION OF TRANSPLANTED KIDNEY AS A FACTOR AFFECTING THE LONG-TERM OUTCOME

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ABSTRACT

The initial graft function is a prognostic indicator for the results of renal transplants. Cold ischemia time and older age of donors have been already well-determinated as risk factors of delayed graft function (DGF), following both deceased- and living-donor kidney transplants. Diagnosis of DGF is closely associated with an inferior long-term outcome. It has been evidenced that graft function and survival rate are significantly worse in transplants with DGF than in those with IGF. Also an acute rejection episodes occur more often in DGF recipients. There are still not enough studies on predictive factors of immediate graft function (IGF), especially in living-donor kidney transplants. Therefore, determining predictors for IGF would be a useful tool to specify the criteria of the most suitable living donor selection.

BACKGROUND

Kidney transplant as an option of renal replacement therapy is an option limited by the number of organs available for transplants and strictly depends on the will of the person who agrees to donate their organs after death. In the case of living donations, healthy volunteers take the risk of the surgical procedure without any direct medical benefits for themselves. Therefore, the expectations of positive long-term results of living donor kidney transplants are higher, and also particularly justified. The initial graft function is a recognised prognostic indicator for the results of renal transplants. Diagnosis of delayed graft function (DGF) is closely associated with an inferior long-term outcome. Risk factors for DGF, following both deceased- and living-donor kidney transplants, have been already well-determined. Although there are numerous data regarding the outcomes of the transplantation procedure, there are not enough studies on predictive factors of immediate graft function (IGF), especially in living-donor kidney transplants.

DEFINITIONS

DGF definition in the literature has not been unified yet. It is commonly identified as the requirement for dialysis in the first week after transplantation. In fact, even this straightforward definition has some drawbacks resulting from different criteria for dialysis prescription. An additional issue are pre-emptive transplants. Definition based on serum creatinine (SCr) level reduction is useful in such cases. Delayed graft function in pre-emptive transplants is usually diagnosed if SCr level on postoperative day (POD) 2 is higher than 0.9 of its pre-transplant value. Transplants with a fast recovery of renal function and satisfactory diuresis are commonly defined as immediate graft function (IGF) cases. However, the criteria for classifying a case as IGF are even more inconsistent. A decrease in serum creatinine level below 3 mg/dL in postoperative day 5 is the most common criterion [2], [3]. Some authors have tried to overcome all those limitations and create an objective tool to define graft function. In 2002, Govani et al. proposed defining IGF versus DGF, based on a 24-hour urine creatinine excretion (UC2) on postoperative day 2 and serum creatinine reduction ratio (CRR2) from POD 1 to POD 2 [4]. They specified the criteria for IGF as having UC2 >1000 mg and CRR2 >30% (calculated according to the following formula: CRR2 = ([SCr1 - SCr2] x 100)/SCr1, where SCr1 and SCr2 represent serum creatinine levels at 24 and 48 hours after transplantation, respectively). Severe DGF - with creatinine clearance of 25 ml/min on postoperative day 7 and/or dialysis within the first week of transplantation - was defined as UC2 ≤1000 mg and CRR2 ≤30%, in contrast to mild DGF - with creatinine clearance of 25 ml/min on or before POD 7, and no need for dialysis - which was defined as UC2>1000 mg and CRR2 ≤30%. Later, creatinine reduction ratio on day 2 was also confirmed by other authors as a useful marker to identify initial graft function [5], [6]. Some other definitions have also been proposed to determine immediate graft function; however, they are much less common in the literature. Certain researchers have identified IGF if SCr level was lower than 2.5 mg/dL at POD 7 in nondialysed patients [7], or if serum creatinine decrease by >20% was detected in the first 24 hours post-transplant [8]. For the clinical purpose, intermediate cases were additionally specified as slow graft function (SGF) subgroup. These are the patients whose initial graft function was not good enough to be qualified as IGF, but sufficient to avoid dialysis (too good to meet DGF criteria). Normally, SGF group includes recipients without the need for dialysis, but with SCr >3 mg/dL when measured on POD 5 [3]. Some studies also use the definition of SCr higher than 2.5 mg/dL on POD 7 in non-dialysed patients [7]. Certain inaccuracies in terminology among the researchers can also be found. SGF subgroup is sometimes called as mild DGF or non-dialysis requiring DGF (ND-DGF), in comparison to dialysis-requiring delayed graft function (D-DGF), which is understood as severe DGF or DGF itself.

FREQUENCY

Delayed graft function has been reported at a variable frequency after deceased-donor (DD) renal transplants, mostly ranging from 20 to 29% (with some deviations of 10% to 50%) [9]–[12]. It is estimated to occur, on average, in 23% of cases in the USA (according to UNOS data) and in up to 30% in European centres [7]. The incidence of clinical symptoms of DGF is much less frequent after living-donor (LD) transplants. Despite their generally well-known better outcome, LD kidney transplants are not completely devoid of DGF risk. The frequency of delayed initial function after LD transplants is also globally diversified. It is reported in.5 – 5 % of recipients [13], [14] or even in up to 10% in some studies, regardless of the procurement technique (laparoscopic vs. open) [12], [15]–[17].

A certain proportion of the remaining recipients has a lower degree of initial graft dysfunction (SGF/ND-DGF). Therefore, it cannot be concluded that 70–80% of kidney transplant recipients have an excellent early functional recovery. The frequency of immediate graft function is estimated at only 44% among deceased-donor kidney recipients [18], and almost 86% among those from living donations [19]. Furthermore, the lack of unified definitions is a serious obstacle in comparing data on the incidence of each type of initial function recovery reported by transplant centres.

PROGNOSTIC FACTORS

There are many factors that may affect the results of kidney transplants. In most studies, deceased-donor kidney transplants were evaluated. Cold ischemia time (CIT) has been shown to be strongly associated with delayed graft function. The rate of DGF transplants with a CIT longer than 24 hours is significantly higher than of those with a shorter CIT [1]. Ojo et al. found the risk of DGF to be increased by 23% for every 6 hours of cold preservation [11]. Also, the old age of the deceased kidney donor is a known risk factor for DGF. Non-

immediate function was significantly more frequent if the donor was over 60 [1], [20] or even over 50 years old [21]. Besides, cerebral haemorrhage as the cause of brain death and preoperative donor serum creatinine were found to be independently related to an increased risk of DGF [10], [22], [23]. Donor- and organ-related factors seem to be the most important predictors for initial graft function. Hetzel et al. revealed that DGF occurred much more frequently in those recipients whose kidney partner also developed DGF [1]. In spite of that, organ recipient-related factors are not completely negligible. Several groups have already found out that also the recipient's high level of preformed cytotoxic antibodies is associated with a higher DGF rate [11], [24]. The analysis performed by Matas et al. showed that the level of panel reactive antibodies (PRA) >10% is a significant threshold value [21]. Accordingly, as it could be expected, the greater rate of DGF has been noted in repeat transplant recipients [23]. Moreover, preoperative dialysis time longer than 12 months significantly impacts the incidence of DGF [19], [22]. The absence of intraoperative diuresis was observed as a prognostic factor for the development of DGF as well [23]. A high incidence of delayed graft function in HIV-infected kidney transplant recipients has also been noted [25].

There were no differences found between transplants from multiorgan vs. only kidneys procurement in terms of DGF occurrence [1]. The risk of DGF seems not to be influenced by recipient's age and body mass index (BMI) [22], second warm ischemia time (whether longer than 30 minutes or not) and perfusion solution (Euro-Collins, Custodiol or UW) [1]. However, the opposite result of the multivariate analysis was also published, showing that recipient's age and their smoking habit affect early graft function [10]. Moreover, vascular anastomosis time was much longer in DGF patients, but multivariate analysis model has not confirmed it as an independent risk factor [10]. The importance given to HLA-ABDR matching has also changed over the last decades. Several studies revealed that the improvement in the deceased donor-recipient HLA match is correlated with a better outcome [26]–[29]. At the same time, the opponents reported satisfactory results of poorly matched recipients, suggesting that other factors should be prioritised in organ allocation [30], [31]. This issue has not yet been resolved. Although the well-matched kidneys with 0-1 mismatches present better long-term outcomes, HLA-ABDR lesser matching was found marginally significant [21], [32]. Various contradictory reports on the relevance of donor's catecholamine use for the incidence of DGF were also published. Some authors concluded that vasopressor support increases the risk of DGF [33], [34]; however, exactly opposite results have also been reported [1], [35], [36] thus the issue remains controversial.

A much smaller number of studies on predictors of the immediate graft function have been published. Similarly, most of them were performed in a group of DD recipients. As Messa et al. have proved, IGF occurs more frequently in younger than in older donor kidney recipients (56.6% if below 60 years old vs. 34.9% if above) [37]. As a predictive factor of IGF, shorter CIT has already been defined [18]. It should be emphasised that the non-delayed graft function cannot be directly associated with IGF. Those with slow initial kidney function recovery (but in the absence of indications for dialysis) are in the intermediate group. Humar et al. used a multivariate analysis to characterise whether risk factors for SGF differ from risk factors for DGF [32]. They concluded that predictors of SGF are very similar and include donor's old age and kidney preservation time longer than 24 hours [32]. This should not be surprising, as SGF represents, in fact, represents a part of the continuum of graft injury, and the degree of initial graft dysfunction is a consequence of the degree of initial graft damage. If so, similar risk factors for both SGD and DGF may be expected. However, Humar and colleagues revealed in their multivariate analysis that recipient's high PRA and donor's elevated SCr level (>1.7 mg/dL) before procurement are certain risk factors for DGF, but not for SGF [32]. In contrary to IGF, SGF group of patients was also found to have higher rates of cadaver donors and male recipients, but no significant differences in numbers of HLA mismatches and age (of both donors and recipients) were observed [38].

It is well known that the outcomes of deceased-donor kidney transplants are not identical to living-donor and cannot be compared. Deceased donation itself is closely related to a greater risk of DGF. Due to a significantly smaller frequency of DGF diagnosis in living-donor kidney recipients, a smaller number of studies on the risk factors for this cohort have been carried out. So far, some data were published that identify recipient overweight and warm ischemia time as risk factors for the incidence of poor (non-immediate) early graft function in living donor kidney transplants [19]. Older age of living donors, like for deceased ones, was assessed to be related to initial delayed graft function [39]. The recipient's higher body weight and higher body mass index [14], [40], male gender [14] and diabetic aetiology of the renal disease [14], [41] also proved to be related to an increased risk of DGF. Moreover, LD kidney recipients with DGF were found to be more sensitised and more HLA mismatched [14]. Unrelated renal donation was also evaluated as a factor of DGF occurrence [41]. Certain authors identified the female LD gender, multiple renal artery grafts and retransplantation as factors associated with a higher risk of DGF upon the univariate analysis; however, multivariate analysis models have not confirmed it [13], [42]. Some other factors were investigated for their possible impact on initial LD graft function. Inflammatory markers, vascular anastomosis time, duration of pretransplant dialysis and AB0 compatibility have been already analysed; however, no clear conclusions were drawn [13]. There is also a reasonable suspicion that higher pre-donation glomerular filtration rate (GFR) of the living-kidney donor correlates with the frequency of immediate graft function, but this still needs to be further evaluated. A number of researchers are concerned that laparoscopic living-donor nephrectomy may be related to a greater risk of DGF, which could predispose to poorer long-term results. However, no significant differences

between open and laparoscopic procurement were found in terms of DGF frequency, as well as long-term graft function and survival [15]. Few studies of immediate graft function in LD have been published so far. Predictors of excellent recovery have not been well investigated yet.

SHORT-TERM OUTCOMES

The association of initial kidney allograft function with the result of transplantation has been analysed in detail. Short-term clinical outcomes of grafting procedure are adversely affected by DGF. DGF diagnosis is usually related to a prolonged time of hospitalisation [10]. Accordingly, it facilitates infections and impairs patient rehabilitation. Performing an allograft biopsy to rule out rejection, usually takes a few extra days. Anti-rejection treatment, if needed, additionally extends the initial hospital stay. Prolonged surgical recovery is closely related with additional diagnostic radiology examinations and laboratory tests. Readmission rates were also found to be slightly higher in the DGF group. Moreover, the lower graft survival rates are related to patient's quicker return to dialysis. It leads to a higher direct cost of initial hospital care. The post-transplant dialysis therapy itself – necessary for patients with DGF but not for those with immediate function – has accounted for 1/3 of the incremental cost [24]. Due to a higher graft failure rate, overall costs increase as well [1], [10].

LONG-TERM OUTCOMES

Although delayed graft function is a complication of early post-transplantation period, it has a significant impact on long-term clinical results of the procedure [1]. It has been evidenced that acute transplant rejection occurs more often in grafts with initial delayed function than in those with immediate recovery [11]. However, the impact of DGF may be masked due to frequent co-occurrence of acute rejection (AR) episodes, which per se can adversely affect the outcomes [37], [43]–[45]. For sure, the presence of both the delayed function and early acute rejection exerted an additive adverse effect on allograft survival [11]. Many authors have also noted the importance of DGF for long-term graft survival [1], [44], [46] and concluded that it was significantly affected by transplant initial function. Kidneys with DGF have a higher rate of graft loss than kidneys with IGF [11]. A significant difference in 1-year [24] as well as 5-year [11] and 7-year graft survival, depending on whether the graft functioned immediately, was observed [1]. Negative impact of delayed function was even evaluated to be more severe than that of poor HLA matching. Ojo et al. assessed the 5-year graft survival rate in HLA-mismatched kidneys without DGF being significantly higher than that of zero-mismatched kidneys with DGF [11]. Moreover, data show that grafts from living donors, even if unrelated and with poor HLA compatibility, have a better short- and long-term prognosis than cadaver grafts with a good HLA matching [47]. Study performed by Narayanan et al. revealed that DGF in living-donor kidney recipients impacts patient survival as well. They analysed a cohort of 44,630 LD recipients and concluded that the death rate with a graft function was significantly higher in those with DGF diagnosis [48]. DGF has a negative effect in terms of AR and graft survival also in LD group [7], [13]. Early mild graft dysfunction after transplantation (irrespective of the name - SGF, PEGF or ND-DGF) can impact long-term graft survival as well [18]. It is a condition related rather to DGF than IGF, and an intermediate outcome of this group was established not to be as good as in patients with IGF, but not as poor as those with DGF [49]. It has been reported that graft survival is significantly lower among the recipients with SGF in comparison to IGF group. A slow reduction of creatinine levels in initial post-transplant period inluences both 1-year and 5-year graft survival rate, independently of the need for dialysis [32], [37], [38], [49]. An increased risk of early acute rejection in comparison to recipients with IGF was also confirmed for SGF cases [32]. However, AR rate was found to be significantly lower at 12 months post-transplant as compared to DGF rates [32]. The incidence of biopsy-proven chronic rejection was similar in recipients with SGF and DGF by 10 years post-transplant and significantly higher than in IGF group [32]. Moreover, graft loss due to acute or chronic rejection was found to be significantly more common in recipients with non-IGF. The function of the kidney graft is also affected by its initial recovery. Both serum creatinine level at discharge and mean SCr level 1 year post-transplant are higher if SGF occurred (vs. IGF) [32].

Accordinng to Messa et al., the diagnosis of immediate graft function may have a different effect on renal allograft outcome depending on several variables, including the age of the donor [37]. They noticed that IGF was associated with a lower SCr level at 6 and 12 months after transplantation among the older donor graft recipients, without any important difference between ND-DGF and D-DGF. The same trend was observed in the young donor group after 6 months. At month 12, no difference in serum creatinine level was further found in IGF vs. ND-DGF subgroups, while D-DGF was associated with the highest SCr levels. A good correlation between CRR2 and renal function throughout the first posttransplant year was also observed by other authors [2], [4], [6]. IGF recipients have also shown a significantly lower risk of graft loss in comparison to non-IGF patients, regardless of the age of the organ donor [2], [10], [37]. In the living-donor cohort, both rejection-free and long-term graft survival rates are significantly higher among IGF recipients (vs. poor early graft function) as well [19].

CONCLUSIONS

The rarity of delayed graft function diagnosis in living-donor kidney recipients may lead to problem marginalisation. However, the initial graft function pattern has the same important impact on long-term outcomes and the consequences are no less serious in this cohort than in deceased-donor ransplant recipients. The incidence of DGF is not a fixed value and it is important to try to prevent post-transplant non-immediate early graft function. Apart from avoiding long ischemia time, minimalisation of any additional risk should be regarded as an important target. Therefore, determining predictive

factors for IGF would be a useful tool to specify the criteria of the most suitable living kidney donor selection, and to ensure the best long-term outcomes of transplantation procedure.

CITE THIS AS

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ABBREVIATIONS

AR – acute rejection
BMI – body mass index
CIT – cold ischemia time
CRR2 – serum creatinine reduction ratio
DD – deceased-donor
D-DGF – dialysis-requiring delayed graft function
DGF – delayed graft function
GFR – glomerular filtration rate
IGF – immediate graft function
LD – living-donor
ND-DGF – non-dialysis requiring delayed graft function
POD – postoperative day
PRA – panel reactive antibodies
SCr – serum creatinine
SGF – slow graft function
UC2 – 24-hour urine creatinine excretion on postoperative day 2

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WHAT DO POLISH MOTHERS KNOW ABOUT BREASTFEEDING?

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ABSTRACT

Breastfeeding up to the sixth month of a child's life is a "gold standard" recommended by the World Health Organisation. According to the Polish Central Statistical Office, in 2014 more than 90% of women breastfed during the first days after delivery, but only 46% continued it beyond the sixth week postpartum. The aim of the study was to assess the knowledge of Polish women about breastfeeding. A prospective cross-sectional study was performed among Polish women who were breastfeeding at the time. The self-composed questionnaire consisting of 23 questions regarding demographic characteristics and knowledge about lactation was distributed via Internet in 2017. A total of 761 women participated in the study. 77% of the respondents have learned about lactation from the Internet. Only 8% indicated doctor consultation as the source of knowledge regarding lactation. The question about the impact of the used medicines on lactation was answered correctly by most of the respondents (97%). On the other hand, the question concerning supplementing the mother's diet with iodine was the most difficult for the respondents to answer (68% of incorrect answers). The correctness of answers was correlated with parity, but not with place of residence or with age. The knowledge about lactation among Polish women is not satisfactory. More focus should be put on well-maintained education measures with the involvement of doctors, midwives, and the media.

BACKGROUND

The World Health Organisation recommends breastfeeding infants for the first six months of their life to achieve optimal growth, development, and health. After this period, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods, with breastfeeding continuing for up to two years of age or even beyond [1]. Breastfeeding offers numerous benefits for infants and their mothers. The cells, hormones, and antibodies in breastmilk improve the baby's immunological response. It has been proven that breastfed babies are subject to lower risks of asthma, leukaemia, and obesity during childhood [2]. According to recent studies, the Sudden Infant Death Syndrome occurs with a lower rate among newborns and toddlers when they are breastfed [3]. What is more, breastfeeding lowers the risk of various health problems among mothers, such as Type 2 diabetes and various types of breast and ovarian cancer, also assisting their recovery following childbirth [4]. According to the Polish Central Statistical Office, in 2014 more than 90% of Polish women breastfed their children during the first days after the delivery, but only 46% of them continued it beyond the sixth week postpartum [5]. Discontinuation of breastfeeding may be caused by the mothers' insufficient knowledge about the benefits it provides. The aim of the study was to assess the knowledge of Polish women about breastfeeding.

MATERIAL AND METHODS

A prospective cross-sectional study was performed among Polish women aged 18 to 45, who were breastfeeding at the time. The self-composed questionnaire consisted of 23 questions. It was distributed via Internet between February and March 2017. The first part of the questionnaire regarded demographic characteristics such as age, place of residence, and parity. In the second part, questions were asked regarding the respondents' knowledge about the impact of a number of factors (breast size, kind of delivery, taken medicines, and others) on lactation, as well as the supplementation of vitamins during breastfeeding. The respondents scored 1 point for a correct answer, 0 points for an incorrect one.

A statistical analysis was performed with the use of the Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables. P value <0.05 was considered significant. *Statistica* software and *Microsoft Excel* were used to compile the database and conduct the analysis.

RESULTS

A total of 761 breastfeeding Polish mothers participated in the study. The most numerous group was mothers aged 26-30 (335, or 44%). 61% of the questionnaires (457) were completed by primiparas. One third of the respondents lived in cities of more than 500,000 inhabitants. Basic characteristics of the study group are provided in Table 1.

Only one respondent answered all questions correctly. One mistake in total was made by 15 mothers (or 2%), while 48 of them did not know the correct answer to exactly two of the questions (6%). 20 women chose wrong answers for more than 50% of the questions (3%). The lowest score achieved was 6 points.

The most popular source of knowledge about lactation among the respondents was the Internet. 77% (586) of the mothers declared it as the first option when looking for information regarding lactation. Women also often indicated consultations with midwives (411, or 54%) and family advice (304, or 40%) as the most popular sources of information. Only 8% of respondents (61) derived their knowledge regarding lactation from doctor consultations. The statistical breakdown of the provided answers is presented in Figure 1.

All the questions analysed in the questionnaire were divided into those with the prevalence of correct answers, those with the prevalence of incorrect answers, and those with similar percentages of correct and incorrect answers. The greatest proportion of correct answers was observed for the question about the impact of the used medicines on lactation (738, or 97% of correct answers). The same result was observed for the question regarding the influence of the breast size on lactation (738, or 97%). 94% of the respondents (715) answered correctly the question about the impact of colostrum on a new-born baby's health. The questions that turned out to be the most difficult for the respondents concerned the supplementation of the mother's diet with iodine and the necessity to eat more than usual during breastfeeding. Almost 60% of respondents (457) provided wrong answers to both of that questions. Questions with the greatest divergence of answers were: "Does the kind of childbirth (natural or C-section) have an impact on lactation?"(373, or 49% of correct answers), "Should a breastfeeding mother supplement her diet with folic acid?" (380, or 50% of correct answers), and "Should a breastfeeding mother supplement her diet with vitamin D?" (388, or 51% of correct answers).

The comparison of the patterns regarding the proportion of correct and incorrect answers given for every question according to the mothers' characteristics was made. The percentage of correct answers given appeared not to depend on age and place of residence. The respondents answered correctly about two thirds of all questions independently of age and place of residence. The results are presented in Figures 2 and 3. According to our analysis, only parity significantly influenced the correctness of the provided answers. Multiparas provided correct answers to a significantly higher percentage of questions. Statistically significant differences in the percentage of correct answers between primi- and multiparas were observed for the questions concerning the supplementation of the breastfeeding mother's diet with vitamin D (63% for primiparas vs. 71% for multiparas; p=0.04), the necessity of eating more than usual during breastfeeding (37% for primiparas vs. 45% for multiparas; p=0.03), and the necessity to supplement the diet of the breastfed child with iron (48 % for primiparas vs. 55% for multiparas; p=0.01). The percentage of correct answers according to parity is presented in Figure 4.

DISCUSSION

According to the results of the study, the most popular source of knowledge regarding lactation among Polish breastfeeding women is the Internet. It can be assumed that the respondents indicated the Web as the primary source to obtain that kind of information because of the great availability of this medium. However, the Internet was not always so widely used to seek information about breastfeeding. In a 2004 study by Jarosz et al., only 2.8% of the respondents indicated it as a source of knowledge about lactation [6], compared to 77% in the study conducted for the purposes of this paper. According to the results, less than one in ten women asked a doctor about breastfeeding. This trend was also observed in a previous study conducted by Klejewski et al. (2012) [7], whereby 11.9% of the respondents provided a similar answer. Birth schools are now more popular (38%) than they were in the past few years (24% in 2004 according to Jarosz et al.) [6].

Our results show that the knowledge about breastfeeding largely depends on the parity of respondents. It seems that the most important factor is the mothers' own experience: having given birth to and raised at least one child, they have better knowledge regarding breastfeeding than primiparas. It might also mean that women do not seek enough information on lactation during the time of their first pregnancy. Parity was also an important factor determining the level of knowledge about breastfeeding according to the results of a 2007 study by Cierpka [8]. The level of knowledge about breastfeeding did not depend on the age of the mother. Similar results were presented by other authors [6,8]. The results of this study, similarly to those of Jarosz (2004) [6], show that the respondents' place of residence is also not correlated with the percentage of correct answers given.

The vitamins and minerals taken by a breastfeeding mother have a great influence on the child's development [9]. The Polish Society of Paediatrics, Gastroenterology, Hepatology, and Nutrition recommends the supplementation of vitamin D in the dose of 1500-2000 IU per day for breastfeeding mothers [10]. Only 51% of the respondents knew of the necessity of taking this vitamin during lactation. The mother's diet should also be complemented with docosahexaenoic acid (200mg/day, or 400-600 mg/day when also eating a small portion of fish) [10]. For the relevant question, 68% of the answers provided were correct. According to the mentioned recommendations, the diet of a breastfeeding mother should provide 290µg of iodine (only 32% of the respondents knew about this recommendation). The respondents also indicated the need of supplementing folic acid and vitamin K during breastfeeding, which is not included among the recommendations of the Polish Society of Paediatrics, Gastroenterology, Hepatology, and Nutrition [10]. According to the results of the study presented in this paper, the level of knowledge about this aspect of breastfeeding is not sufficient among women, as for most of the questions concerning this issue, a great variety of answers was given, which indicates that the cited recommendations should be more widely propagated among Polish mothers.

The choice between breastfeeding and formula feeding should be the mother's own decision. Many factors may influence the period of time during which mothers should breastfeed. However, it is very important to spread the knowledge regarding lactation among pregnant and breastfeeding women, so that the only reason why the child is not breastfed would not be the mother's insufficient knowledge about lactation.

CONCLUSION

The knowledge about lactation among Polish breastfeeding women is not satisfactory. More focus should be put on well-maintained education with the involvement of doctors and midwives, as well as with the cooperation of various media. Medical staff should also indicate reliable online sources of knowledge, as the Web seems to be the easiest way to educate young mothers.

CITE THIS AS

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AGE	LESS THAN 20	21-25	26-30	31-35	36-40	41-45
	1% (n=11)	16% (n=120)	44% (n=334)	31% (n=236)	6% (n=48)	2% (n=12)
PLACE OF RESIDENCE	COUNTRYSIDE	CITY WITH LESS THAN 50 000 CITIZENS	CITY WITH 50 000 -100 000 CITIZENS	CITY WITH 100 000-500 000 CITIZNES		CITY WITH MORE THAN 500 000 CITIZENS
	22% (n=165)	12% (n=94)	13% (n=101)	18% (n=139)		34% (n=262)
PARITY	PRIMIPARAS		MULTIPARAS			
	61% (n=464)		39% (n=297)			

FIG. 1. SOURCE OF KNOWLEDGE ABOUT LACTATION AMONG POLISH BREASTFEEDING MOTHERS.

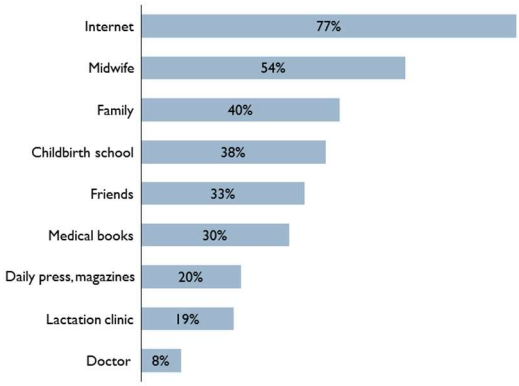


FIG. 2. PERCENTAGE OF CORRECT ANSWERS ACCORDING TO THE PLACE OF RESIDENCE OF RESPONDENTS.

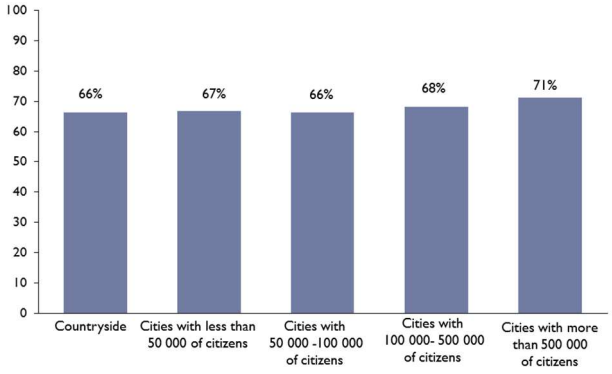


FIG. 3. PERCENTAGE OF CORRECT ANSWERS ACCORDING TO THE AGE OF RESPONDENTS.

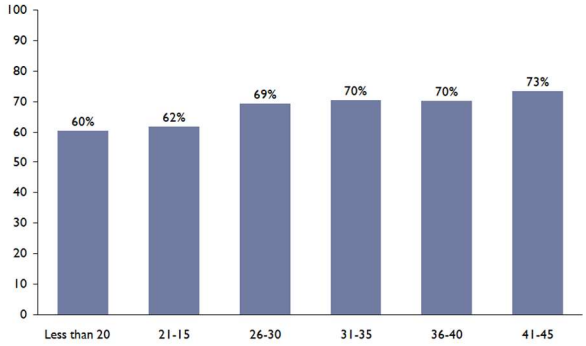
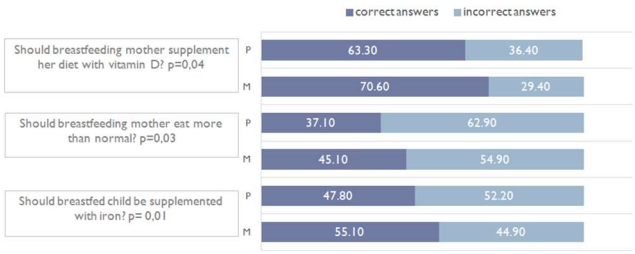
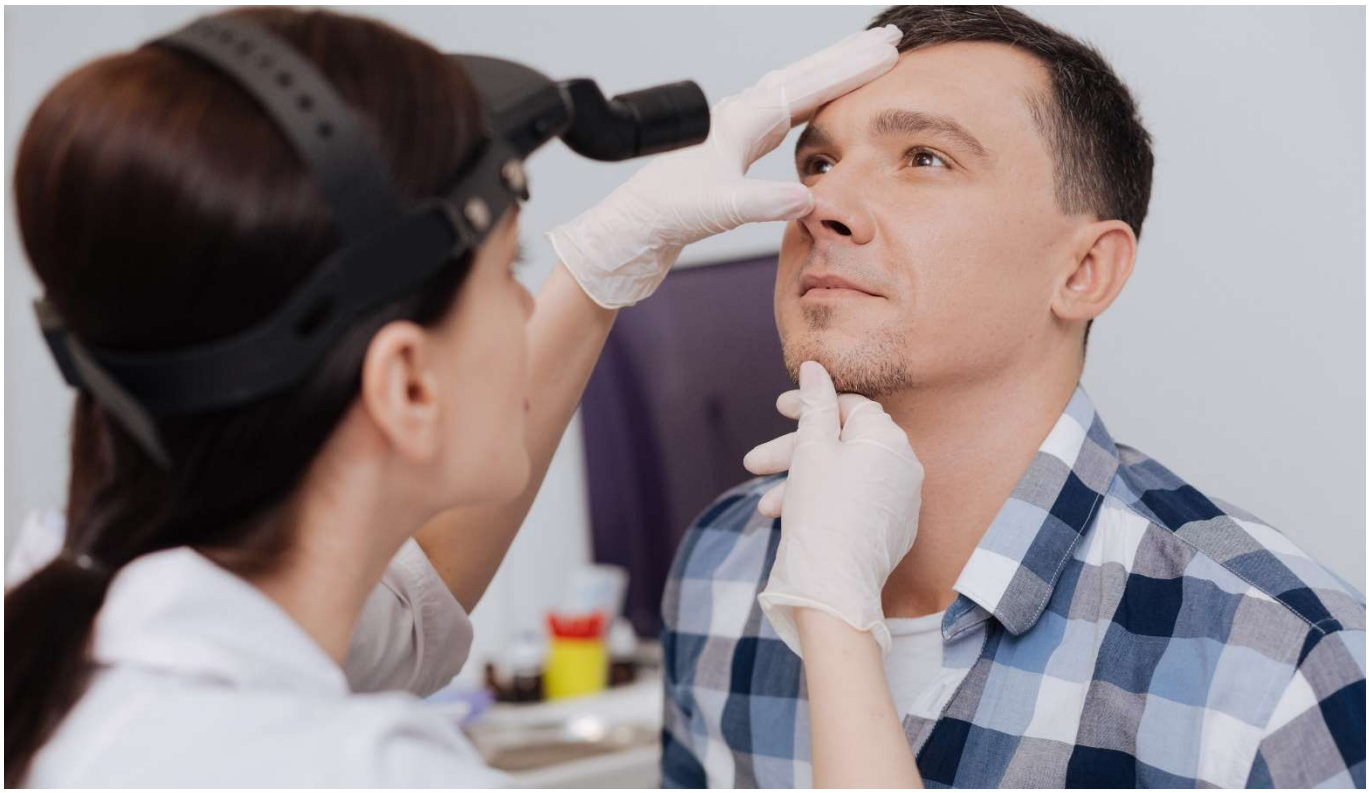


FIG. 4. PERCENTAGE OF CORRECT ANSWERS ACCORDING TO THE PARITY OF RESPONDENTS (SELECTED QUESTIONS).



p-primiparas, m-multiparas



EAR, NOSE AND THROAT MANIFESTATIONS IN PATIENTS WITH RHEUMATIC DISEASES

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WORD COUNT	2062
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ABSTRACT

Different ear, nose and throat (ENT) symptoms may appear in cases of several rheumatic diseases (RD). The aim of our study was to find the most common ENT manifestations in patients with RD; to find RD which began with ENT symptoms; to reveal possible associations between age, gender, ENT symptoms and complications among patients with RD. A retrospective study was conducted by analyzing records of patients who were hospitalized in Rheumatology and Otolaryngology departments of Pauls Stradinš Clinical University Hospital. The data obtained were statistically processed using IBM SPSS Statistics 22.0 software. 434 patients were viewed retrospectively: 23.7% males (n=103) and 76.3% females (n=331). 9.2% of patients with RD (n=40) had ENT manifestations, among which the most frequent RD were: granulomatosis with polyangiitis (GPA), systemic sclerosis and systemic lupus erythematosus. The most frequent ENT symptoms among patients with mentioned RD were respectively: chronic otitis media, xerostomia and oral ulcerations. Complications were observed in 37.5% (n=15) of patients with ENT manifestations. In six patients RD began exactly with ENT symptoms. ENT manifestations and complications were statistically significantly more often in men and in both genders of the age group 31- 40 ($p<0.05$). ENT symptoms are not common among patients with RD but they can be quite characteristic and may appear as the first symptoms of specific RD, such as GPA. Timely recognition of ENT symptoms related to RD is important to avoid complications, start early management of RD and to improve life quality of patients.

BACKGROUND

Rheumatic diseases are a diverse group of diseases that commonly affect the joints, rarely muscles and internal organs. In case of several rheumatic diseases, anatomical structures of ear-nose and throat (ENT) system also may be affeced by the autoimmune process that can result in different ENT manifestations. Generally otolaryngological symptoms are not common among patients with rheumatic diseases, so this is the reason why they remain a diagnostic challenge for the rheumatologists, the otolaryngologists, and the general practitioners [1]. It has been reported that sometimes ENT symptoms may be the initial sign of otherwise asymptomatic or undiagnosed rheumatic disease [1].

The aim of our study was to find the most common ENT symptoms in patients with rheumatic diseases; to find rheumatic diseases which began with ENT symptoms; to reveal any possible associations between demographic parameters, ENT diagnoses and complications among patients with rheumatic diseases.

MATERIAL AND METHODS

A retrospective study was conducted by analyzing records of the patients who were hospitalized in Rheumatology and Otolaryngology departments of Pauls Stradinš Clinical University Hospital in the period from January 1, 2014 to October 31, 2016. Based on the literature [1-5] and experience of the specialists from aforementioned departments, the following diagnoses with possible ENT manifestations were included and reviewed in the study: granulomatosis with polyangiitis (GPA, prev. Wegener's granulomatosis), systemic lupus erythematosus (SLE), systemic sclerosis, polymyalgia rheumatica, dermatomyositis, polymyositis, eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss syndrome) and relapsing polychondritis. ENT manifestations and complications, demographic data such as age and gender were recorded.

Statistical analysis was conducted using IBM SPSS Statistics 22.0 software. Descriptive Statistics, Chi-Square Test and Fiser's Exact Test were used. The significance level was set at maximum of 5% ($p < 0.05$).

The study was approved by two local ethical committees: The Ethics Committee of Riga Stradinš University and The Ethics Committee for Clinical Research at Development Society of Pauls Stradinš Clinical University Hospital.

RESULTS

434 patients were viewed retrospectively - 23.7% males (n=103) and 76.3% females (n=331). The mean age was 54.11 years, the median 56.00 years, SD=15.90 years, the minimum 18 years, the maximum 87 years.

Altogether there were 35.7% of patients with SLE (n=155), 25.6% of patients with systemic sclerosis (n=111), 20% of patients with polymyalgia rheumatica (n=87), 8.1% of patients with polymyositis (n=35), 7.1% of patients with GPA (n=31), 1.8% of patients with dermatomyositis (n=8), 1.4% of patients with EGPA (n=6) and one patient with relapsing polychondritis.

9.2% of patients with rheumatic diseases (n=40) had ENT manifestations. The most frequent of those rheumatic diseases were GPA, systemic sclerosis and SLE (highlighted in Fig. 1).

The frequency of ENT manifestations among patients with GPA, systemic sclerosis and SLE is seen in Fig.2.

Patients with GPA as the most common ENT symptoms had chronic otitis media and chronic rhinitis. The following otolaryngological problems in patients with GPA were diagnosed less frequently: chronic sinusitis, otitis media with effusion, hypoacusis, nasal septum destruction or perforation and nasal septum deviation.

Patients with systemic sclerosis experienced such ENT manifestations as xerostomia, chronic rhinopharyngitis and chronic laryngitis.

In patients with SLE the most common were oral ulcerations. Other ENT manifestations in patients with SLE were rare and seen equally frequently - hypoacusis, chronic sinusitis, chronic rhinopharyngitis, nasal septum deviation, oral candidasis and chronic rhinitis.

Rarely ENT symptoms were noted in patients with dermatomyositis, polymyalgia rheumatica and EGPA.

In the study there were only 3 patients with dermatomyositis who had any ENT manifestations. Each of them had otitis media with effusion, also there were one case of oral ulcerations and one case of cronic rhinopharyngitis.

Both of the patients with EGPA had chronic sinusitis and one of them additionaly had chronic otitis media.

In patients with polymyalgia rheumatica following ENT manifestations were noted - chronic laryngitis, nasal septum deviation, chronic rhinitis and chronic otitis media.

Also there was one case of relapsing polychondritis - a rare rheumatic disease which primarily affects cartilage of the ear and nose but also potentially affects the eyes, tracheobronchial tree, heart valves, kidneys, joints, skin, and blood vesels [6]. That patient had a fast progressing autoimmune hearing loss (initially unilateral, then bilateral) and episodic vertigo. The disease started with hoarsness followed by breathing difficulties because of the destruction and collapsing of the laryngeal cartilages. Despite the agressive antiinflammatory therapy, an autoimmune leasion of the inner ear occur. The envolvement of nose cartilages resulted in saddle-nose deformity. Due to breathing problems and total deafness, tracheostomy and cochlear implantation were performed.

ENT complications were observed in 15 patients (37.5%) with rheumatic diseases having any ENT manifestations. Most often complications were found in patients with GPA - 7 patients had hearing loss (conductive or sensorineural) and 3 patients had nasal septum destruction or perforation. Three patients with systemic sclerosis had dysphagia due to xerostomia. One patient with polymyalgia rheumatica had chronic suppurative otitis media and one patient with EGPA had unilateral sensorineural hearing loss.

Rheumatic diseases in 6 patients began exactly with the ENT symptoms. In most of those cases GPA was diagnosed (4 patients). Those patients as the first symptoms had frequent nose bleeding, nasal congestion

and hypoacusis with pressure or pain in the ear. In one more patient, SLE began with oral ulcerations and in the other patient relapsing polychondritis began with unilateral hearing loss and episodic vertigo.

Analysis of possible association between demographic parameters, ENT diagnoses and complications among patients with rheumatic diseases revealed that male gender was statistically significantly related to the presence of ENT manifestations (Pearson Chi-Square Test, $p = 0.001$) and complications (Fiser's Exact Test, $p = 0.011$).

The age group 31 – 40 years in both genders was also statistically significantly related to the presence of ENT manifestations (Pearson Chi-Square Test, $p < 0.001$) and complications (Fiser's Exact Test, $p = 0.003$).

DISCUSSION

For many times, ENT manifestations are overlooked by both the patient and the physician because the attention is drawn to the particular or life threatening internal organ manifestations of rheumatic diseases.

In our study the mean age of patients is 54.11 years which is similar to other studies which report the mean age of 52.1 years [4]. Also the majority of patients were females, which is simi¬lar to previous studies [2, 4].

According to *Harris J, et al.* the prevalence of ENT symptoms in patients with GPA at the onset of disease is 70% and the prevalence during the course of diseases was reported to be up to 90% [2].

In our study only 7.1% of rheumatic patients (n= 31) had GPA.

The authors of several sources [1, 2, 5] suggest that the most frequent otologic condition in patients with GPA is conductive hearing loss resulting from granulomatous nasopharyngeal involvement, followed by Eustachian tube dysfunction and serous otitis media. The middle ear is affected in at least one-third to one-half of all patients, which is similar in our results – chronic otitis media was seen in 11 of 31 patients with GPA.

The paranasal sinuses, most commonly the maxillary and ethmoid sinuses, are affected in at least two-thirds of patients [2] which differ from our findings - chronic sinusitis was found only in 4 of 31 patients with GPA. Also another study suggests that chronic sinusitis is most frequently seen ENT manifestation in GPA patients followed by recurrent oral ulcers, while spontaneous septal perforation is the most infrequently seen symptom [3].

Other potential symptoms in GPA patients could be crusting, pain, epistaxis, ulceration in nasal mucosa, collapse of the nasal bridge ('saddle nose' deformity), which may occur due to nasal chondritis [2] or nasal septum perforation [1].

According to *N S Jones* [7], over 50% of patients with GPA have nasal symptoms and signs at the presentation; nasal obstruction and discharge are most common of them. Our study revealed that only in 4 of 31 patients GPA initially presented with ENT symptoms. Nose bleeding, nasal congestion and hypoacusis were the most common of them.

Severe subglottic stenosis causing severe acute dyspnea and requiring tracheostomy has been described in patients with GPA [1]. Subglottic stenosis occurs in about 20% of these patients [2].

Kopf A, et al. suggests that in GPA patients the following symptoms can be found: facial/cranial pain (23.1%), rhinorrhoea (46.2%), otorrhoea (30.8%), dyspnoea/dysphonia (15.4%), and recurrent epistaxis (15.4%) [4].

Unfortunately, only few authors cover systemic sclerosis in their researches. There are reports about quite different ENT related manifestations from our study – telangiectasias on the palate, oral mucosa, and tongue, nasal perforation [2]. Trigeminal neuropathy has also been demonstrated in patients with systemic sclerosis [1].

In our study, the most common ENT related manifestation in patients with SLE was oral ulcerations. These results coincide with other studies and literature [1, 8, 9]. The authors mention, that oral ulcers in SLE, usually, but not invariably painless, are characteristically localized on the soft and hard palate [1]. Other authors mention another oral ulcer placement - also on the tongue and buccal mucosa [2]. There are reports about hyperkeratotic, lichen planus–like plaques on the buccal mucosa and palate, tinnitus with or without hearing loss, nasal and auricular chondritis. These reports are summarized in *Harris J, et al.* work [2].

Gera C and *Kumar N* in their study about understanding and practice of various ENT problems of rheumatic diseases among otolaryngologists concluded, that otolaryngologists are aware of ENT manifestations of rheumatic diseases but their index of suspicion, practical implication of knowledge and confidence for evaluation of such diseases is low [3]. This may result in delayed patient referring for appropriate evaluation and management of possible rheumatic diseases.

In our study we assessed the frequency of ENT manifestations and complications among patients with rheumatic diseases, as well as found associations of them with gender and age.

The results of our study could be helpful in proper management of patients with suspected rheumatic diseases either by otolaryngologists, rheumatologists or general practitioners, especially in cases of granulomatosis with polyangiitis, systemic sclerosis and systemic lupus erythematosus in which ENT related manifestations according to our study may be present.

More studies are needed to describe the current state of the art of otolaryngology manifestations of autoimmune diseases and to improve knowledge about rheumatic diseases among the physicians.

CONCLUSIONS

According to the results of our study, ENT symptoms and complications in patients with rheumatic diseases statistically significantly more often are seen in men and in both genders of the age group 31-40. This fact should be kept in mind by physicians because timely recognition of ENT manifestations related to rheumatic diseases is important to avoid complications, to start early

management of rheumatic diseases and to improve the life quality of patients.

ENT symptoms and manifestations are not common among patients with rheumatic diseases but they can be quite characteristic and may appear as the first symptoms of specific rheumatic diseases, especially in case of granulomatosis with polyangiitis.

Further studies are necessary for a full assessment of the clinical profile of ENT manifestations of rheumatic diseases.

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ABBREVIATIONS

ENT – ear, nose and throat
EGPA – eosinophilic granulomatosis with polyangiitis
GPA – granulomatosis with polyangiitis
RD – rheumatic diseases
SLE – systemic lupus erythematosus

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FIG. 1. PATIENTS WITH RHEUMATIC DISEASES WHO HAD ANY ENT MANIFESTATION.

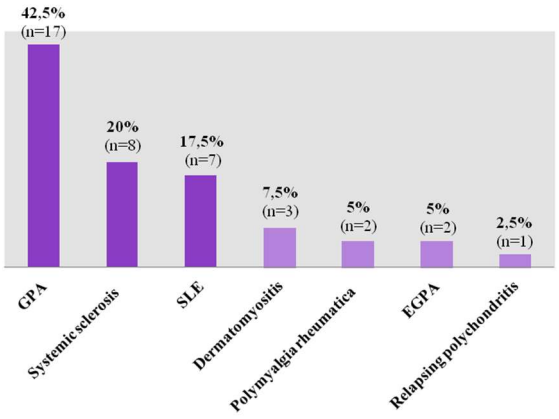
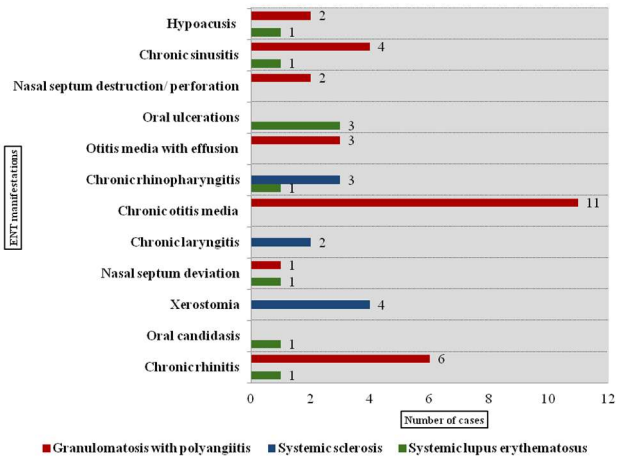


FIG. 2. FREQUENCY OF ENT MANIFESTATIONS AMONG PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS, SYSTEMIC SCLEROSIS AND SYSTEMIC LUPUS ERYTHEMATOSUS.



SYPHILIS IN PREGNANCY – CASE REPORTS, REVIEW OF THE LATEST GUIDELINES AND PREVENTIVE STRATEGIES

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CONFLICT OF INTERESTS	no conflicts of interest

ABSTRACT

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. It is of special concern during pregnancy because can lead to adverse pregnancy outcomes and congenital syphilis. We present two cases of such complication during pregnancy. The first patient was a 26-year-old female G2P2, positive for CMV IgM, HCV, rubella and VDRL, who reported to the hospital at 30 weeks of gestation with lower abdominal pain. PPROM was diagnosed and cesarean section had to be performed due to non-reassuring CTG tracings and breech presentation of the fetus. Alive son was born (1600 g /46 cm, 4-6-7 points Apgar score) with respiratory failure, ascites and anorectal obstruction. The newborn was found to be negative for CMV and HCV, whereas positive for rubella and syphilis. Treatment with crystalline penicillin was administered. The second 20-year-old primiparous pregnant female was referred to the hospital at 39 weeks of gestation due to suspected fetal hypotrophy. The patient had early latent syphilis, diagnosed and treated during the first trimester. Cesarean section was performed due to vulvar and anal genital warts. A healthy daughter was born (3080 g /52 cm, 10 points Apgar score). Due to the lack of documentation regarding treatment of maternal syphilis, crystalline penicillin was administered to the newborn. Screening and early penicillin treatment are the most important factors that can eliminate complications related to the prenatal contagion with *Treponema pallidum*. Yet despite the lack of treatment or its inappropriate administration, the pregnancy complicated with maternal syphilis may end in a completely different way.

BACKGROUND

Syphilis is a systematic, sexually transmitted disease (STD) caused by the spirochete *Treponema pallidum* which leads to dysfunction of various organs. This disease is of special concern during pregnancy because causes adverse pregnancy outcomes, including stillbirth, prematurity, low birth weight and congenital syphilis in children [1, 2]. It is obligatory to screen pregnant women for syphilis. If it is early diagnosed, it is well treated and may not affect the fetus [3]. Despite raising awareness about the problem of STDs, syphilis in pregnancy and congenital syphilis (CS) remain an important issue in Europe and all over the world [4].

We present two cases of syphilis diagnosed during pregnancy with a different course of the disease, as well as a review focusing on this STD - its epidemiology, manifestation, diagnosis and treatment - based on the latest guidelines, together with possible preventive strategies.

CASE 1

A 26-year-old female G2P2 had already been found to be positive for CMV IgM, HCV, rubella and VDRL, for which the patient was neither furtherly diagnosed nor treated. Being at 30 weeks of gestation the patient reported to the hospital with lower abdominal pain. USG scan revealed fetal ascites with centralization of his circulation. The patient did not consent to be hospitalized and left the unit on her own request, coming back after a few hours with Preterm Premature Rupture of Membranes (PPROM) and labor in progress. Cesarean section was performed due to non-reassuring CTG tracings and breech presentation of the fetus. A son was born, weighing 1600 g and having 46 cm in length, assessed as 4-6-7 points of the Apgar score. The newborn was in a serious condition, had respiratory failure requiring intubation and artificial ventilation, also presented ascites, anaemia, thrombocytopenia and anorectal obstruction. Due to the latter, he was immediately transferred to the Anaesthesiology and Intensive Care Unit of the Pediatric Hospital, where the surgery for the congenital malformation was performed two days after birth. A double colostomy was pulled out, whereas the radical surgery has been scheduled for the fourth month of the newborn's life. Moreover, the surgery of inguinal hernia was performed and the child was diagnosed with hypospadiasis and retinopathy of prematurity (stage 2). The echocardiography examination revealed narrowing of the pulmonary trunk, which could be related to the congenital rubella.

The diagnostic process of congenital infections was also performed. The newborn was found to be negative for CMV and HCV, whereas positive for rubella with level of IgG = 153 and IgM = 1.95. Also the syphilis infection was confirmed with positive blood tests: FTA 1:900, FTA-ABS, USR 2+, VDRL 1:2, TPHA 3+ and CSF tests: FTA 1:10, TPHA 1:4. Due to the lack of mother's presence and no possibility to compare the results of the mother and the child, the serological diagnosis was difficult. The child did not present any symptoms of congenital syphilis. Nevertheless, the treatment with crystalline penicillin was administered for 10 days.

CASE 1

A 20-year-old primiparous pregnant patient was referred to the hospital at 39 weeks of gestation due to suspected fetal hypotrophy. The patient had gestational diabetes, pathological obesity (BMI>40) and early latent syphilis, which was diagnosed during the first trimester and treated for 2 weeks with crystalline penicillin, yet without any documentation regarding the treatment and its results. Due to genital warts of the vulva and the anus cesarean section was performed. A healthy daughter was born, weighting 3080 g and having 52 cm in length, assessed as 10 points of the Apgar score. The newborn was in a general good condition, yet the USG scan revealed bilateral thalamic vasculopathy and physical examination showed clubfeet which was more expressed on the left side. After the orthopaedics consultation, a plaster cast was applied. The X-ray of long bones showed no abnormalities and ophthalmologic examination was without deviations. From the second day of life, jaundice was observed but did not require any medical intervention.

Due to the lack of documentation regarding the treatment of maternal syphilis, crystalline penicillin was administered to the newborn for 10 days. Serological tests revealed that the mother was positive for VDRL (tire 1:4), FTA-ABS, FTA 1:1300 and TPHA, whereas the child was positive for VDRL (tire 1:2), FTA 1:450 and TPHA and negative for IgM test. The cerebrospinal fluid examination revealed no abnormalities with negative VDRL test. Congenital syphilis was excluded. The mother and the newborn were discharged on the 13th day postpartum with the recommendation of orthopaedic control of the newborn's hip joints, ophthalmological control for 6 months and control of the syphilis treatment for 3 months.

DISCUSSION

Epidemiology

Syphilis is still a widespread, significant disease. In 2007 World Health Organization (WHO) implemented a project "The global elimination of congenital syphilis" in order to eradicate it. Due to WHO efforts between 2008-2012, the number of maternal infections decreased from 1.4 million to 930 000, whereas adverse pregnancy outcomes decreased from 520 000 to 350 000. Most significant decline was observed in the South-East Asia Region. In Africa syphilis is the most common disease transmitted transplacentally, however decline in that region was negligible. In Europe, the number of maternal infections almost halved, from 35 349 to 18 437 and the number of adverse pregnancy outcomes decreased from 7 837 to 4 307. Antenatal Care (ANC) syphilis testing is the most effective way of preventing horizontal spread. In 2014, 85.5% of pregnant women worldwide were tested. The median syphilis prevalence among the ANC attendants was 0.7% and the median treatment rate among affected

was 95.5%. Despite public awareness of STDs, syphilis rate is still unsatisfactorily high [4].

Clinical manifestation

Syphilis can be transmitted during sexual activity. Cervical changes that occur during pregnancy, such as hyperaemia, eversion and friability, may facilitate the contagion [5]. The incubation period varies from 10 to 90 days (average about 3 weeks) [6]. Syphilis can be divided into several stages: primary, secondary, latent and tertiary syphilis and all the women who are screened as positive should be staged based on the history and physical examination [7]. The clinical manifestation of the acquired syphilis is not apparently altered by pregnancy, yet syphilis may have a significant impact on the fetus due to the risk of transplacental infection [2]. Spirochetes are able to cross the placenta and infect the fetus from the 14th week of gestation and the risk increases with gestational age [8]. The transmission can occur at every stage of maternal disease, yet the highest risk is within the first four years after maternal acquisition of the *T. pallidum* in the absence of treatment [9]. The manifestation of clinical infection also depends on the immunological response of the fetus because all symptoms result from the robust inflammatory response to the presence of spirochaete. That is why the symptoms are more severe after 20th weeks of gestation as the fetal immune system is more developed [10].

The risk of transplacental infection of the fetus exceeds 50% in the primary and secondary untreated syphilis, amounts to 40% in early latent syphilis and equals 10% in late untreated syphilis [10]. Moreover, adverse pregnancy outcomes are 12 times more frequent in women with syphilis than in general population [1]. In those untreated, frequency of adverse pregnancy outcomes amounts to 76.8% [11]. The infection can result in congenital syphilis (36.6%), stillbirth (26.4%), premature delivery (23.2%), miscarriage (14.9%), low birth weight (23.4%) and perinatal death (16.2%) [11]. Children who survive may present various symptoms of early or late congenital syphilis. The early congenital syphilis concerns changes that appear within first 2 years of child's life, out of which the most common are: abnormal bone X-ray (61%), hepato- and splenomegaly (51% and 49%), petechiae (41%) and skin lesions (35%). The late congenital syphilis includes features that appear after 2 years of life, such as frontal bossing (30-87%), palatal deformation (76%), dental dystrophies (55%) or interstitial keratitis (20-50%) [5].

Diagnosis

Every pregnant woman should be screened for syphilis because in most cases screening with appropriate treatment prevents adverse outcomes in the mother and the child [12, 13]. The diagnosis should be known in the first trimester as most fetuses become infected after 20th weeks of gestation, whereas treatment before this period usually helps preventing congenital disease [3]. It is recommended to repeat tests in the third trimester (28 - 32 gestational weeks) and at the delivery in case of risk factors or local epidemiology [3, 7].

Screening test can be either nontreponemal test (NTT) or treponemal test (TT) or both of them, depending on the preference of the laboratory standards and local epidemiology [3, 7]. Nontreponemal tests are based upon the reactivity of serum from infected with syphilis patients to the antigens containing cardiolipin, lecithins, and cholesterol. These tests include: Venereal Diseases Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR). Although they are not specific, they are widely used in screening because of low cost, ease and quickness of performance. Moreover, they allow to monitor the response to the therapy. Treponemal tests detect an interaction between serum immunoglobulins and treponemal antigens which make them more specific than NTT. However, they should not be used to monitor disease activity or treatment efficacy, because they usually remain positive for lifetime. Treponemal tests include: Fluorescent Treponemal Antibody Absorption test (FTA-ABS), Treponema pallidum Haemagglutination test (TPHA), Treponema pallidum Passive Particle Agglutination test (TPPA) and Enzyme Immunoassay/ Chemiluminescence Immunoassay (EIA/CIA) [14]. Both treponemal and nontreponemal tests can give false positive results. In NTTs, it can occur during pregnancy, acute febrile illness or recent immunization, while TTs can be false positive in Lyme disease, leptospirosis and other diseases caused by *Treponema spp* or in autoimmune diseases [15].

Therefore, due to the possibility of false-positive test results, every reactive screening test requires confirmation. The result of the TT should be verified by another TT and quantitative NTT. The result of NNT should be confirmed by TT and quantitative NNT [3]. The diagnostic interpretation of syphilis serology in pregnant women does not differ from the serology results of other patients [7].

The NNT screening test can be false positive with low titer in pregnant woman. This situation can be considered if the confirmatory TT is negative, the patient is asymptomatic and has low risk of acute syphilis. Follow-up is not required during pregnancy, yet it is required 4 – 6 weeks after delivery with TT and NNT [7].

The diagnosis of congenital syphilis is difficult because maternal IgG antibodies (both nontreponemal and treponemal) are able to pass through placenta, which complicates the interpretation of serological tests in newborns (1,7). Nevertheless, all neonates born to mothers with reactive NTT and TT should be tested with quantitative NTT (VDRL or RPR) performed in the child's serum, because umbilical cord blood can be contaminated with maternal blood and lead to false-positive results (7). The congenital syphilis is highly probable, if the serologic titer is fourfold higher than the mother's titer [1, 3, 7]. It is not recommended to perform TT because of the difficulty of interpretation as well as IgM tests due to the lack of sensitivity [7].

The physical examination of those neonates should also be performed in order to detect features of congenital syphilis e.g.: hepatosplenomegaly, jaundice, ascites, rhinitis, skin lesions [1, 7]. Recommended laboratory tests include: complete blood count, liver tests, electrolytes, biochemical and serological evaluation of cerebrospinal fluid. X-ray of long bones should be also performed and in some cases ophthalmologic examination is required [3, 7, 16]. Detection of *T. pallidum*

by darkfield test or PCR in placenta, autopsy material, skin lesions or body fluids (e.g. nasal discharge) should also be considered [3, 7].

Treatment

The only known effective drug for preventing maternal transmission to the fetus and treating fetal infection is penicillin G [2, 17]. Pregnant women should be treated with the first line therapy option which is benzathine penicillin G (BGP) in a dose appropriate for the stage of the disease and if allergic to penicillin, they should be desensitized [2, 3, 17]. Penicillin desensitization is a relatively safe procedure that can be performed orally or intravenously. The patient is exposed to a small dose of penicillin which is gradually increased until an effective level is reached. Then the appropriate therapeutic penicillin regimen must be maintained. Non-penicillin regimens (erythromycin, ceftriaxone, azithromycin) are not recommended for pregnant women and should be considered only if penicillin is not accessible or when penicillin desensitization in allergic patients is not possible [7].

For early syphilis, a single dose of 2.4 million units intramuscular (IM) is sufficient yet sometimes it can be indicated to administer second dose of BPG 1 week after the initial dose [2, 3, 17]. Treatment for late latent syphilis or latent syphilis of unknown duration is BPG 2.4 million units IM weekly on day 1, 8 and 15 [2, 3]. Second line therapy option is procaine penicillin 600.000 units IM daily for 10–14 days, if BPG is not available [3].

Any neonate who has confirmed or presumed congenital syphilis should be treated with aqueous crystalline penicillin G 100.000 – 150.000 units/kg/day administered as 50,000 units/kg/dose intravenous (IV) every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days. Second option is procaine penicillin 50.000 units/kg IM daily for 10 - 14 days [3, 18]. When congenital syphilis is less likely, the single dose of BPG 50.000 units/kg IM should be administered [18]. No treatment is required with unlikely congenital syphilis, yet infants with reactive nontreponemal tests should be followed up serologically to ensure whether the patient undergoes seroreversion [18]. However, some recommendations claim that all neonates born to syphilis seropositive mothers should be treated with a single dose of BPG 50.000 units/kg IM, regardless of whether the mother was treated during pregnancy or not [3].

Although penicillin is still effective, clinically important resistance to macrolides, a second-line alternative to penicillin, has occurred. Rapid spread of these resistant spirochetes combined with global persistence of syphilis show that T. pallidum can develop resistance to tetracycline, an alternative antibiotic, and to penicillin, the recommended first-line antibiotic for syphilis treatment [19].

Understanding the need for syphilis screening

Management of pregnant patients predisposes physicians to reduction of infection rates due to cessation of both horizontal and vertical transmissions. In 2012, reported number of worldwide maternal infections was as high as 930,000 cases [4]. Apart from cessation of infection spreading, prenatal care helps avoiding adverse pregnancy outcome as prevention of congenital syphilis infection decreases the risk of premature birth, stillbirth, low birth rate, and infant mortality [20-24]. At the same time, once detected syphilis is an easily treatable disease and a lot of harm can be prevented by means of adequate management [25, 26]. Even though the WHO launched in 2007 a global initiative to eliminate cases of congenital syphilis, we are still witnessing infants exposed to risk of avoidable infections [27]. This means additional efforts and new approaches are more than welcome. It seems that screening in pregnancy is still the key to successful prevention [28]. As the percentage of screened pregnant women in the US is about 80%, there is still possibility of enhancing screening programs in order to reach women without access to adequate prenatal care, which is the main risk factor for skipping syphilis screening [29]. Another example comes from China where premarital screening strategies were found effective [30]. Therefore, combination of both – premarital and pregnancy screening possibilities is worth considering. Another lesson coming from presented case reports is the need for careful documenting of every syphilis screening and treating history. Lack of proper information may cause chaos or lead to further and more dangerous shortcomings. Patient with no clear evidence of previous management should be treated as a patient with no history of management at all.

CONCLUSIONS

Syphilis during pregnancy is still considered as a worldwide public health problem. Screening combined with early penicillin treatment are the most important factors that can eliminate complications related to prenatal contagion with *Treponema pallidum*.

CITE THIS AS

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ABBREVIATIONS

ANC – Antenatal Care
BMI – Body Mass Index
BPG – Benzathine Penicillin G
CMV – Cytomegalovirus
CS – Congenital Syphilis
CSF – Cerebrospinal Fluid
CTG – Cardiotocography
EIA/CIA – Enzyme Immunoassay / Chemiluminescence Immunoassay
FTA-ABS – Fluorescent Treponemal Antibody Absorption
HCV – Hepatitis C Virus
IM – intramuscular
IV – intravenous
NTT – Nontreponemal Test
PCR – Polymerase Chain Reaction
PPROM – Preterm Premature Rupture of Membranes
RPR – Rapid Plasma Reagin
STD – Sexually Transmitted Disease
TPHA – Treponema pallidum Haemagglutination
TPPA – Treponema pallidum Passive Particle Agglutination
TT – Treponemal Test
USG – Ultrasonography
VDRL – Venereal Diseases Research Laboratory
WHO – World Health Organization

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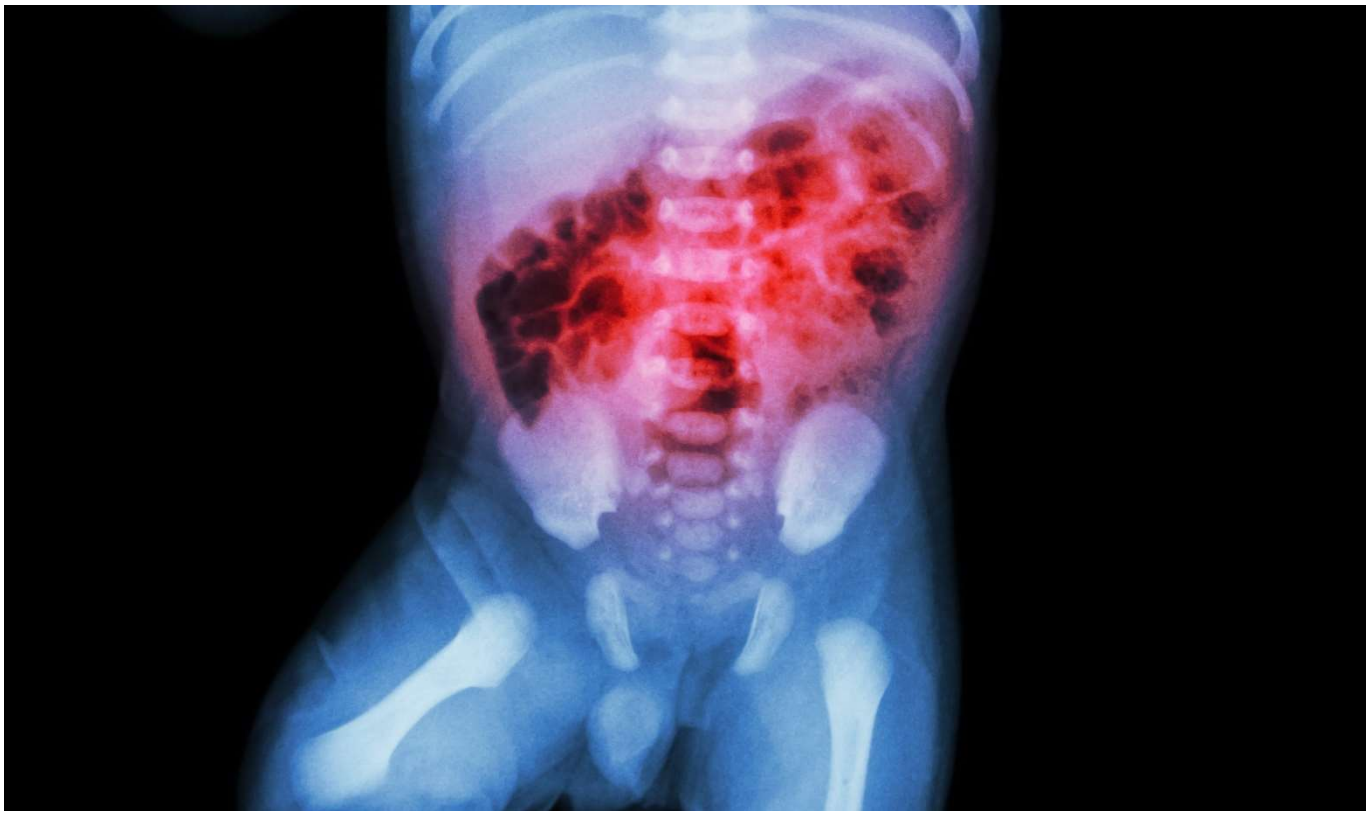

NECROTIZING ENTEROCOLITIS IN LATVIA BETWEEN 2012 - 2016

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CONFLICT OF INTERESTS	no conflicts of interest

ABSTRACT

Necrotizing enterocolitis (NEC) is the most common gastrointestinal surgical emergency in the neonatal period, with prematurity as the single most important risk factor. The overall reported incidence is 0.1% of all live births, and 3-12% of very low-birth-weight infants (<1500g). NEC typically occurs in the first few days of life with the initiation of enteral feedings. Treatment consists of orogastric tube decompression, broad-spectrum antibiotics and in advanced cases - surgical management. A retrospective study was made including medical history data from all NEC patients in Neonatal Intensive Care Unit in Riga, from year 2012 to 2016. Results: In the time period from year 2012 to 2016 there were 84 cases of NEC. The overall incidence of NEC in Latvia was 0.08% of all live births, and 7.5% of very low-birth-weight infants. Almost all of the patients (90.5%) were born premature. The average onset of NEC was at the age of 7.7 days. Out of all cases – 27.4% of patients had no data of NEC in abdominal x-ray and/or ultrasound and only 23.8% had intestinal pneumatosis. Using Bell's staging criteria 25% of the patients were classified as Stage III – advanced NEC. In 73.8% of cases the treatment was nonsurgical – including antibiotics and orogastric tube decompression. NEC was more common in preterm neonates and those with very low-birth-weight – the same as mentioned in literature. The most commonly used treatment was nonsurgical, as there were only 25% of patients with Stage III – advanced NEC, therefore it is important to diagnose NEC as early as possible.

BACKGROUND

Necrotizing enterocolitis (NEC) is the most common cause of gastrointestinal-related morbidity and mortality in neonatal intensive care units. NEC usually occurs in infants born at ? 35 weeks of gestation without any other underlying conditions, therefore prematurity is known as the single most important risk factor [1].

The overall reported incidence of NEC is 0.1% of all live births, and 3-12% of very low-birth-weight infants (<1500g) [2]. Although rarely NEC can be also seen in term and late-term infants, particularly in those who have underlying conditions, e.g. cyanotic congenital heart disease, respiratory distress syndrome, gestational diabetes mellitus, intestinal atresia, intestinal aganglionosis etc. [1, 3, 4].

In premature infants NEC typically occurs in the first few days of life when the enteral feedings are initiated. That is when the intestinal lumen first becomes colonized with bacteria [5]. The diagnosis of NEC is based on Modified Bell's Staging Criteria for Necrotizing Enterocolitis – consisting of history, clinical examination and radiologic findings [2]. The symptoms of NEC are usually nonspecific and include feeding intolerance, abdominal distention, occult or gross blood in stool etc. [1, 2].

In all stages of NEC, the first and most important part of the treatment is nil per os (i.e. complete bowel rest with orogastric tube decompression) and broad-spectrum antibiotics. In more advanced cases of NEC, when there is bowel perforation, surgical management is needed. It is estimated that around 20-40% of infants will require urgent surgical intervention. Laparotomy with resection of ischemic bowel and creation of enterostomies is known as the traditional surgical approach [2,6]. As an alternative approach – primary peritoneal drainage can be done and it has been proved to have no significant differences in mortality compared with those infants who underwent laparotomy [7].

The overall mortality of NEC is 15-30% and it is higher in extremely low-birth-weight infants and those with fulminant NEC (i.e. total necrotizing enterocolitis) [2].
The aim of this study was to find out the incidence of NEC in Latvia and to compare it to the overall incidence mentioned in literature data, also to evaluate the time of diagnosis, imaging results and most frequently used treatment.

MATERIAL AND METHODS

The medical records of 84 NEC patients from Children's Clinical University Hospitals' Neonatal Intensive Care Unit were retrospectively assessed. Analysis included medical records from year 2012 to 2016.

We assessed such parameters as – weeks of gestation, birth weight, sex, age at the time of diagnosis, imaging findings, stage according to Bell's Staging Criteria for Necrotizing Enterocolitis (Table 1), surgical treatment received and the outcome.

Birth weight was defined according to World Human Organization standards:

- Normal birth weight – >2500 g;
- Low birth weight – 1500-2500 g;
- Very low birth weight – 1000-1500 g;
- Extremely low birth weight – <1000 g.

The imaging findings were classified based on the changes in abdominal x-ray and ultrasound:

- 0 – no pathologic changes found on abdominal imaging OR no imaging done;
- 1 – nonspecific changes on abdominal imaging;
- 2 – intestinal pneumatosis;
- 3 – free air and/or fluid in abdominal cavity.

The treatment received was classified by its complicity:

- 0 – no surgical treatment done;
- 1 – peritoneal drainage;
- 2 – resection of the ischemic bowel and enterostomy;
- 3 – peritoneal drainage combined with resection of the ischemic bowel and enterostomy;
- 4 – resection of the ischemic bowel and primary anastomosis.

The incidence of NEC was calculated by using data (i.e. all live births, all premature live births) from Statistical Yearbook of Health care in Latvia 2012 to 2016.

RESULTS

The overall incidence of NEC in Latvia is 0.08% of all live births, which is similar to incidence found in literature data. Almost all of the patients (90.5%) were born premature. NEC is almost 16 times more common in infants born preterm (i.e. <37 weeks of gestation) and the incidence of NEC in this group of infants is 1.3%. Figure 1 shows the overall incidence of NEC compared to incidence in group of infants born preterm.

As suspected – the highest incidence was found in very low birth weight infants (Table 2).

The distribution of NEC in both genders differed in these five years, as it is shown in Figure 2.

The mean age at the time of diagnosis of NEC was 8 days, with minimum of 1 day and maximum of 61 day.

In the time period from year 2012 to 2016 – 27.4% of patients had no data of NEC in abdominal imaging and only 23.8% had intestinal pneumatosis (Figure 3). In year 2015 free air and/or fluid in abdominal cavity was seen in 50% of patients, although in all the other years it was seen only in about 7-18%.

Using Bell's staging criteria 42%, 33% and 25% of the patients were classified as Stage I, II and III. Again – in year 2015 Stage III NEC was seen in 50% (n=6) of patients, although in other years it was not more than 33% (Figure 4).

In 73.8% of cases the treatment was nonsurgical – including antibiotics and orogastric tube decompression. Surgical treatment (i.e. resection of the ischemic bowel and enterostomy or primary anastomosis) was made only in 18 cases. Although one patient did have Stage III NEC, he did not undergo surgical treatment because of his extremely severe condition. Five patients received

treatment with peritoneal drainage. The most frequently used treatment options are shown in Figure 5.

Overall there were 18 cases of *exitus letalis*. In years 2013 and 2014 there was 100% of survival.

DISCUSSION

According to recent systematic review of prognostic studies the most important risk factors for the development of NEC are prematurity and very low birth weight. In this review the birth weight is determined as clinically more important [8]. The results presented in this paper are consistent with works of Clark et al [9] and Llanos et al [10] which confirmed that NEC is most frequently seen in patients born preterm.

Potential risk factors such as race and gender unfortunately are rarely discussed in the literature, although there is some data that affirms that males may have a higher risk of NEC associated death as compared to females [11]. Further studies on race and gender influence on the possibility and outcome of NEC should be made.

Some studies suggest that Bell's staging should be abandoned in favor of a new acquired neonatal intestinal diseases (ANID) taxonomy (e.g. Gordon's classifications), which has the goal to focus on the different etiologies of the ANIDs at the time of diagnosis, not to stage the severity of disease (other than surgery and mortality) [12,13]. In our study 75% of patients were classified as Stage I and II NEC which leads to 73.8% of patients being treated non-surgically. Therefore it seems that the usage of Bell's staging criteria in the preference of treatment given is acceptable and appropriate. The fact that there were only 18 of 84 patients in our study that received surgical treatment shows that the diagnosis of NEC was not delayed in most of the cases.

According to Bury et al some studies have shown that the administration of prophylactic enteral antibiotics in premature infants resulted in reduction of NEC and also NEC-related deaths [14]. Further prospective studies on this topic would be highly recommended to establish guidelines on prophylaxis of NEC in risk groups.

CONCLUSIONS

In our study NEC was more frequently found in preterm infants and those with very low birth weight – the same as mentioned in literature. The most commonly used treatment was nonsurgical, as there were only 25% of patients with Stage III – advanced NEC, therefore it is important to diagnose NEC as early as possible. Further studies on possible prophylaxis of NEC are recommended.

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ABBREVIATIONS

ANID – acquired neonatal intestinal diseases
NEC – necrotizing enterocolitis

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TAB. 1. MODIFIED BELL'S STAGING CRITERIA FOR NECROTIZING ENTEROCOLITIS.

Stage	Classification	Clinical Signs	Radiologic signs
I	Suspected NEC	Abdominal distention Bloody stools Emesis/gastric residuals Apnea/lethargy	Ileus/dilatation
II	Proven NEC	As in stage I, plus: Abdominal tenderness +/-Metabolic acidosis Thrombocytopenia	Pneumatosis intestinalis and/or portal venous gas
III	Advanced NEC	As in stage II, plus: Hypotension Significant acidosis Thrombocytopenia/disseminated intravascular coagulation Neutropenia	As in stage II, plus: Pneumoperitoneum

TAB. 2. INCIDENCE OF NECROTIZING ENETEROCOLITIS BETWEEN DIFFERENT BIRTH WEIGHT GROUPS.

Birth weight [g]	2012	2013	2014	2015	2016
< 1000	10.44	17.54	12.50	4.35	16.67
1000-1500	2.20	5.83	5.26	3.45	5.43
1500-2500	0.27	0.79	0.12	0.25	0.26
> 2500	0.01	0.01	0.01	0.02	0.02

FIG. 1. OVERALL INCIDENCE OF NECROTIZING ENTEROCOLITIS COMPARED TO INCIDENCE IN GROUP OF INFANTS BORN PRETERM.

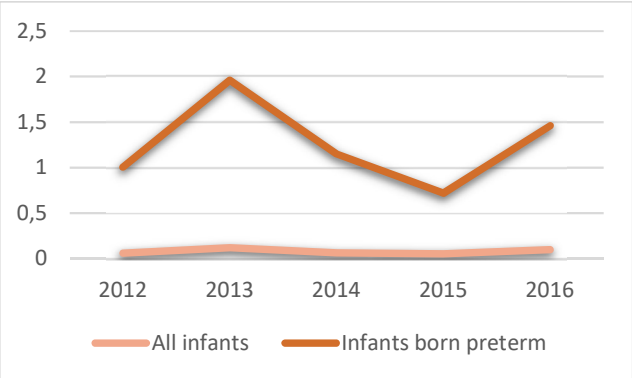


FIG. 2. DISTRIBUTION OF SEX IN PATIENTS WITH NECROTIZING ENTEROCOLIT.

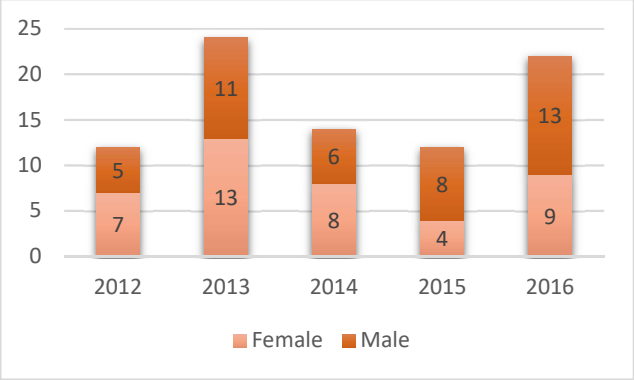


FIG. 3. ABDOMINAL IMAGING FINDINGS IN YEAR 2012-2016.

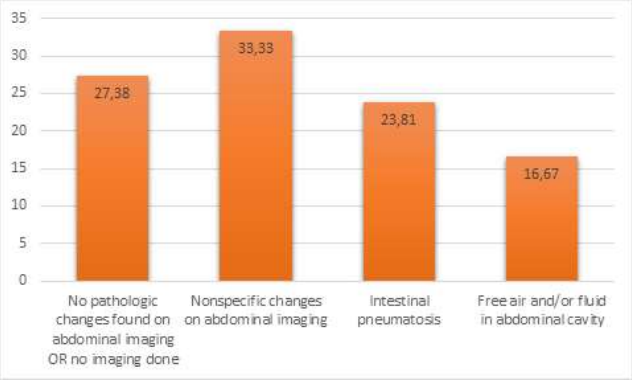


FIG. 4. NUMBER OF PATIENTS ACCORDING TO MODIFIED BELL'S STAGING CRITERIA FOR NECROTIZING ENTEROCOLITIS.

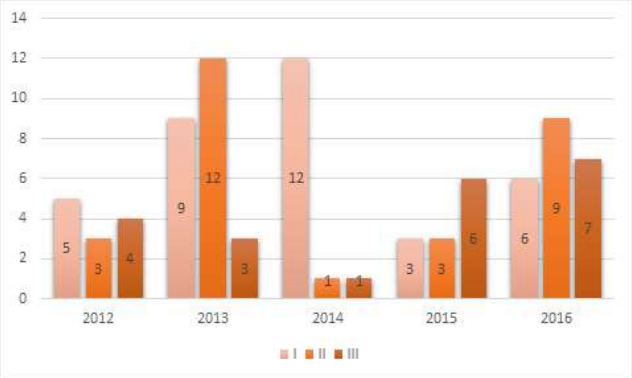
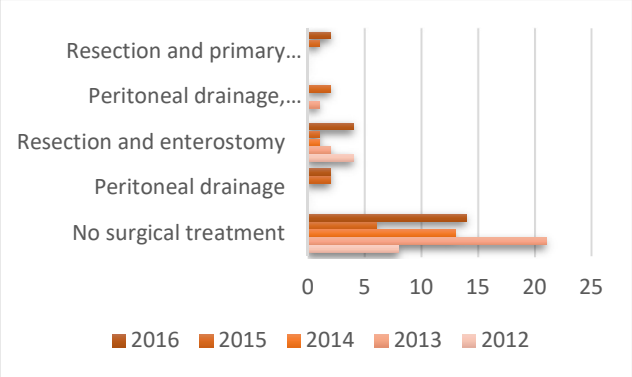
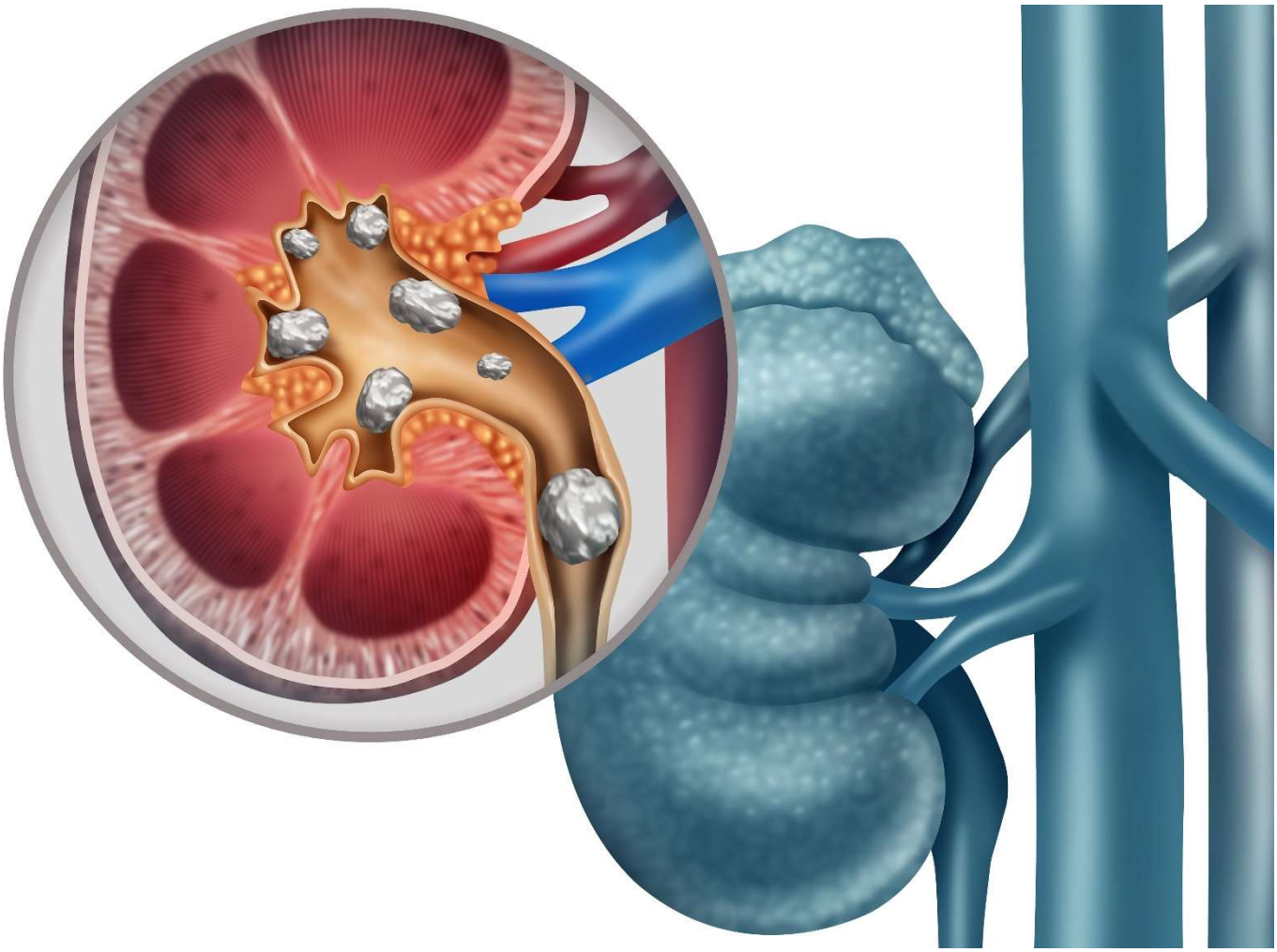


FIG. 5. TREATMENT USED IN CASES OF NECROTIZING ENTEROCOLITIS.





RENAL COLIC IN PREGNANT WOMEN. REVIEW

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ABSTRACT

Renal colic is the most common cause of non-obstetric abdominal pain in pregnant woman and may be an indication for hospitalization. Nephrolithiasis occurs in 1 to 244-2000 pregnant women. Pregnancy is a condition when both physiological and mechanical changes increase the risk of kidney stones. Renal colic in pregnant women is associated with significant potential risk to the mother and the fetus. Diagnosis and management of nephrolithiasis during pregnancy is more complicated than in non-pregnant women. The gold standard in the diagnosis of renal colic during pregnancy is ultrasonography, in special situations other imaging techniques are also used. The first line treatment is usually conservative. If the conservative management fails or is contraindicated, more advanced treatment is used. In this article, we review metabolic changes during pregnancy that may promote renal stones formation, complications associated with acute renal colic in pregnancy and proposal of diagnostic and treatment algorithms for renal colic.

BACKGROUND

Renal colic is the most common cause of non-obstetric abdominal pain in pregnant woman and may be an indication for hospitalization [1]. Diagnosis and treatment of nephrolithiasis during pregnancy is a multidisciplinary challenge. One of most difficult aspects of renal colic management in gravid women is the distinction between physiological and pathological hydronephrosis. One of the key points is the kidney stones treatment optimalization in order to provide the best possible care for future mother's health while minimizing adverse effects on the fetus [1, 2].

EPIDEMIOLOGY

According to the National Health and Nutrition Examination Survey, nephrolithiasis affects 1 in 11 people in society: 10.6% of men and 7.1% of women [3]. A significant increase in the nephrolithiasis occurrence has been more noticeable in recent years, which is related to unbalanced diet, climate change, obesity, as well as the development of diagnostic methods [3-5].

According to different authors, nephrolithiasis occurs in 1 to 244-2000 pregnant women [6]. Kidney stones are more common in multiparous women and 80-90% of cases occur in the 2nd or 3rd trimester of pregnancy [6-8]. According to the study of Swartz and Stothers, nephrolithiasis is more frequent in Caucasian women, with a history of nephrolithiasis or hypertension [9, 10]. Study of Yung-Shin et al. shows that the incidence of stones in both sides is similar, although physiological hydronephrosis usually occurs in the right kidney. This has also been confirmed by other authors [8]. Rosenberg et al. have observed that women with kidney stones were older and more often obese in comparison to those without this condition [11].

CHANGES IN PREGNANCY

Anatomical, physiological and metabolic changes occurring during pregnancy may predispose to the development of renal stones [7, 12]. Enlargement of the upper ureter and pelvicalyceal dilatation up to 2 cm are frequent changes during pregnancy, considered to be physiological. The two abovementioned phenomena are caused by mechanical and hormonal factors [2].

As far as the hormonal factors are concerned, they affect tissues usually in the beginning of pregnancy, during first 6-10 gestational weeks. Circulating progesterone can relax the smooth muscle, reduce peristalsis of the ureters and thereby cause ureteral dilation [12]. Furthermore, as the pregnancy progresses, there is mechanical ureteral pressure by the enlarged uterus, which may also accelerate hydronephrosis [2, 12]. In 90% of pregnancies physiological hydronephrosis affects the right kidney, whereas in 67% - the left one. This results from the fact that the right ureter is more oppressed by the enlarged uterus and ovarian vein and protection of the left ureter by esophageal gas [12].

Physiological ureteric enlargement can result in urinary retention, thus, crystallization and formation of kidney stones occur and may also lead to infection [2, 11, 12].

Renal plasma flow, as well as the glomerular filtration rate, increase during pregnancy by 50%, resulting in increased excretion of calcium, uric acid and sodium - kidney stones components. Calcium tubular reabsorption is also associated with decreased parathyroid hormone secretion. These changes increase the risk of developing nephrolithiasis during pregnancy [2, 13].

Despite the changes in the urinary tract during pregnancy, incidence of renal stones in pregnant and non-pregnant women is similar due to increased secretion of inhibitors of stone formation: citrate, magnesium, and glycoprotein nephrocalcin. Increased urinary alkalinity during gestation also promotes renal stone formation [2, 12].

In general population, 80% of kidney stones is formed with calcium, pregnant women likewise. However, gravid patients' stones are composed of 74% calcium phosphate, whereas in the rest of population it is mainly calcium oxalate. This is most likely due to changes in kidney function and higher urinary pH during pregnancy [2, 12, 14].

SYMPTOMS AND COMPLICATIONS

Attention should be paid to the clinical symptoms of nephrolithiasis. Flank pain occurs in 85 to 100% of patients [2, 6, 8, 15]. Common symptoms include fever, nausea and vomiting [2, 6, 8, 15]. Dysuria and frequent urination are also widespread, especially when a stone is located in the lower part of the urinary tract or with accompanying infection [2]. Patients often have microscopic hematuria, leukocytosis and dysuria. Asymptomatic urinary tract infections are also common [2, 8, 12, 15].

Kidney stones are associated with a number of potential risks, both for the mother and the fetus. Rosenberg et al. evaluated obstetric complications and birth outcomes among women with renal stones [11]. Women with kidney stones, compared to those without them, were at higher risk of recurrent abortions, mild preeclampsia, gestational diabetes and chronic hypertension. Nephrolithiasis was also associated with urinary tract infections, pyelonephritis, hydronephrosis, and hydroureter. No difference in occurrence of premature rupture of fetal membranes or perinatal outcomes (birth weight, Apgar scores or perinatal mortality) was reported. Swartz et al. proved that patients with kidney stones had two-fold risk of premature birth compared to patients without kidney stones (9). Although the data are contradictory, similar complications such as recurrent spontaneous abortions, premature births, premature rupture of membranes, preeclampsia have been reported in many studies [16, 17].

DIAGNOSIS

A general urine test should be performed during diagnostic process of renal colic. Values of urine pH>7 may indicate infection with urea-degrading bacteria and pH <5 may suggest the presence of uric acid stones. Blood tests include complete blood count and creatinine levels [18].

The golden standard in depicting kidney stones in

general population is CT scan, which is a radiation source that has a teratogenic effect on the fetus. Effects depend on radiation dose and fetal age and include fetal death, congenital malformation, and fetal growth restriction [2, 17, 18]. According to the guidelines of the American College of Obstetricians and Gynecologists (ACOG), the dose that is safe for fetus is <50 mGy. The risk of congenital abnormalities increases significantly with the dose >150 mGy. There are many other techniques to diagnose kidney stones in pregnant women, so CT should be performed only in justified cases [2, 19].

Ultrasound is a pre-test for pregnant women because of its safety, widespread availability and lack of ionizing radiation, which is harmful to the fetus. The Food and Drug Administration has proposed an upper limit of 720 mW/cm^2 for the spatial-peak temporal ultrasound of the ultrasound beam for obstetric purposes [2]. Ultrasonography also has its disadvantages. According to numerous studies, the sensitivity of detection of stones in ultrasound differs from 29 to 69%. It is difficult to distinguish physiological hydronephrosis from hydronephrosis caused by nephrolithiasis. In physiological hydronephrosis, ureteral dilation rarely extends below the lower pelvic floor [20]. Transvaginal ultrasound may sometimes be useful for the diagnosis of stones in distal urethra and for verifying unclear diagnosis in transvaginal ultrasonography [20].

During diagnostics, the sensitivity of stone detection can be increased by the use of Doppler ultrasound exam to assess renal vascular resistance. Recently the sensitivity of ultrasound imaging has improved markedly. There are many Doppler ultrasound features which can indicate nephrolithiasis, including elevated resistance index (RI), inter-renal difference in RI, asymmetric absence of the ureteric jet or hydronephrosis. It is worth mentioning that absence of ureteral jet can be false positive because of the compression by the gravid uterus. To avoid the misdiagnosis the absence of ureteral jet should be confirmed in contralateral decubitus patient position [15, 22].

The second radiological examination in the diagnosis of kidney stones in pregnant women is MRI. MRI is performed in case of persistent pain despite conservative treatment [2, 20]. MRI tests provide high quality images of kidneys and urine without ionizing radiation. It uses external magnetic field and radio waves which are safer for the fetus. According to Clements et al. study and the American College of Radiology (ACR), MRI does not cause any harmful effects on the fetus [23, 24]. However, it should not be performed during the first trimester because of the limited data on MRI effect on organogenesis [23]. MRI sensitivity in renal colic diagnosis in general population was 84%, with 100% specificity [21, 26]. There is no clear data on the sensitivity and specificity of the MRI during pregnancy [23]. During the MRI examination, stones in the ureter are not directly visible, but some features that demonstrate their presence can be spotted. Stones appear as a lack of signal against the background of a high urine signal in the ureter. Stones may also be observed as a place of the ureteral occlusion. In case of urolithiasis it often occurs in atypical sites. The advantage of MRI is the possibility of visualizing such complications as pyelonephritis, tumors or anatomical pathology [2, 12, 20, 25, 26].

In recent years, new techniques have been used in colic diagnosis. Regan et al. in their study used non-contrast HASTE MR urography in non-pregnant patients. The sensitivity and specificity of this study was comparable to CT (sensitivity of 84%, specificity of 100%, and accuracy of 86%) [26]. Mullins et al. have proven that HASTE MR can also be effective in the diagnosis in pregnant women as well as in other cases when CT tests using ionizing radiation cannot be performed [27].

In 2016, Egemen Çifçi et al. conducted a study to compare the interobserver variability and the accuracy of magnetic resonance urography (MRU) by using a balanced sectional-turbo field echo (B-TFE) for detecting ureteral calculi in order to determine the magnitude of additional factors (size, density and location of the calculus) on the sensitivity and specificity of the MRU. They showed that B-TFE had lower sensitivity and higher specifity than CT. It is a good alternative for pregnant women who cannot undergo CT [28].

CT is not recommended for the diagnosis of kidney stones during pregnancy because of ionizing radiation. However, some authors recommend low-dose CT as long as the ultrasound examination is not diagnostic. White et al. conducted a retrospective study of 20 patients with a mean gestational age of 26.5 weeks. Each patient had an ultrasound examination performed before a low-dose CT. The average radiation exposure was 705.75 mrads. Presence of stones was reported in 13 out of 20 patients. High sensitivity and specificity of the study were demonstrated. There was no negative impact on the fetus [29].

TREATMENT

Due to the possible complications accompanying pregnancy and the physiological changes, the treatment of pregnant women is complex and requires special effort [30]. In recent years, the diagnosis and treatment of nephrolithiasis have changed dramatically, which is due to the advance of imaging and innovation in treatment. According to the European Association of Urology guidelines, conservative treatment should be the first instance of treatment for all uncomplicated cases of kidney stones, excluding those that have clinical indications for special treatment [30]. Studies indicate that approximately 75-80% of kidney stones in pregnant women undergo spontaneous stone passage [14, 31]. According to Andreoiu et al. 68.5% of patients had spontaneous expulsion of stones [31]. Coll et al. proved in their study that the spontaneous stone passage depends on the size of the stones: for stone 1 mm in diameter it was 87%, for stones 2-4 mm – 76%, for stones 5-7 mm – 60%, for stones 7-9 mm – 48%, and for stones larger than 9 mm – 25% [32].

Conservative treatment should be performed with analgesic, hydration, because many patients experience dehydration due to nausea and vomiting, and antibiotics in case of infection [30]. Hydratation enables the movement of stones by increasing flow and secretion of urine. A great number of drugs used in the treatment of stone disease in the general population is contraindicated

in pregnancy. Pregnant women should avoid nonsteroidal anti-inflammatory drugs as these are associated with premature closure of the ductus arteriosus in utero, oligohydramnios, early spontaneous abortion and cardiac malformations [31].

In case of mild pain, acetaminophen and paracetamol are the best drugs to cure pain since there are no known toxic side effects to the fetus as well as no bleeding predisposition. Opioids are generally used to treat acute renal colic and can be safely used during pregnancy. Morphine sulphate and meperidine in small doses do not have a negative effect on fetus, but their long-term use can lead to fetal narcotic addiction, intrauterine growth retardation (IUGR) and premature labor [31].

Management with expulsive therapy with tamsulosin (alpha blocker) and nifedipine (calcium channel blocker), with or without steroids, facilitates the spontaneous movement of stones in the ureter. In the study of Bailey et al., the group of patients treated with alfa-blocker had a 45% and with nifedipine a 49% higher and faster stone expulsion than the control group. Moreover, patients treated with tamsulosin or nifedipine had lower analgesic requirements, fewer hospitalizations and colic episodes [2, 33]. Bailey et al. revealed that tamsulosin is safe for the mother and the fetus and can be safely used as a complementary therapy for renal disease [34].

Approximately 50% of the patients with stones experience urinary tract infections and require antibiotic therapy. The antibiotics mostly used are penicillin and cephalosporins. Aminoglycosides, chloramphenicol, tetracycline, fluoroquinolones and sulfa drugs are contraindicated in pregnancy due to teratogenic effects on the fetus [32, 36].

If the pregnant women fail conservative management or if it is contraindicated, more advanced treatment is required. Active management include: temporizing measures to relieve obstruction - insertion of a ureteral stent or percutaneous nephrostomy (PCN) tube, or definitive treatment - lithotripsy, percutaneous nepthrolithotomy, or ureteroscopic stone removal (URS) [2, 30].

Urgent decompression of the urinary system to the definitive stone removal is preferred in the presence of febrile, bilateral stone disease, obstetric complications, presentation in the first trimester and patient or surgeon preference [2, 31]. The choice of stent and nephrostomy is often the subject of debates. When it comes to infection, both methods seem similar [2, 31]. A randomized controlled study indicated that ureteral catheters, ureteral stents, and PCNs are equally effective for decompressing the urinary tract [2,37]. PCN is usually preferred in the presence of sepsis, when excessive ureteral manipulation is best avoided [2]. The efficacy of both, stent insertion and PCN in the treatment of kidney stones has been confirmed in several studies. Patients experienced pain relief and effective decompression [8, 36].

Temporary drainage is beneficial, whereas definitive management is contraindicated when the pregnant woman has active infection, abnormal anatomy, bilateral stones, transplant kidney, obstetric complications or when there are inadequate obstetric, endourological or anaesthetic resources available to the patient. Definitive treatment is a reasonable option [30] for the remaining patients, except the first trimester.

Ureteroscopy is a safe and effective method of treating kidney stones in pregnancy. It can be performed under local, regional or general anesthesia. It barely causes complications to the mother and the fetus. Johnson et al. performed 46 procedures in 45 patients. 2 obstetric complications were observed: 1 threatened preterm labor managed conservatively and 1 preterm delivery. There was no fetal loss. No statistically significant characteristics were identified while differentiating those patients, who have obstetric complications [38]. Atar et al. have demonstrated the efficiency and the safety of ureteroscopy during pregnancy [39]. According to the ACOG guidelines for surgery in pregnant women, non-urgent ureteroscopy is best done in the second trimester. The procedure should be performed by a qualified urologist, in a hospital with a neonatal ward, with an obstetrician who would monitor the fetus and that would have the capacity of performing cesarean delivery [32, 40].

Shockwave lithotripsy (SWL) and percutaneous nephrolithotomy (PNL) are contraindicated during pregnancy, because of fetal damage and death observed in animal studies, particularly with exposure later in pregnancy [32]. However, case reports on SWL exposure in unrecognized pregnancy showed no fetal distress [41]. Several case reports have identified cases of successful and safe percutaneous nephrolithotomy (PNL) during all trimesters of pregnancy [31]. Since the introduction of miniaturized instruments, ureteral orifice dilator is not required. The stone can be extracted intact. Holmium laser performs stone disintegration ideally and it was proven safe for the pregnant woman and the fetus [32]. Abedi et al. in their study showed that lithotripsy is safe and effective in pregnant patients with kidney stones [42].

Open surgery should be barely performed unless all other alternatives have been exhausted or when endourology expertise or equipment is not available. Operations performed in previous years resulted in the end of pregnancy in 6.5%, 8.6% and 11.9% of patients, during the first, second and third trimester, respectively [31].

CONCLUSION

Renal colic is a major cause of pain, which is often confused with pregnancy contractions. Kidney stones are a diagnostic and therapeutic problem [44]. It should be remembered that it can cause life-threatening sepsis and also cause complications in both the mother and the fetus. It requires consultation with an urologist, gynecologist and general surgeon to exclude other surgical conditions such as acute appendicitis and a twisted ovarian cyst. One has to remember that because they can threaten the life of the pregnant woman [43].

The preferred method for evaluating renal colic is ultrasonography. However, although it has a high specificity of 90%, the sensitivity of this method is quite low (11% -24%). Also, MRI is a valuable and safe method of imaging during pregnancy to distinguish pathological and physical obstructions. There are many controversies about the use of CT in pregnant women. Concerns about

potential side effects of ionizing radiation should not prevent medically indicated diagnostic procedures using the best available modality for the clinical situation. However, if there are indications for diagnostic procedures that require radiation, various techniques may be used that reduce the radiation dose [29, 43].

There are conflicting views on whether ionizing radiation during pregnancy may increase the risk of childhood cancer, particularly leukemia. However, the potential for carcinoma of the radiation is controversial because non-irradiated siblings of these children also have higher incidence of leukemia [45].

Most of the deposits are discarded spontaneously and in these cases conservative treatment is sufficient. Complications may need insertion of the catheter into the ureter, transcutaneous renal excretion (percutaneous nephrostomy), or removal of the ureterotrophic scars (URS). However, there is a lot of controversy about extracorporeal lithotripsy, which is contraindicated in pregnancy. Research show that laser lithotriper can be used successfully and safely in pregnant women with acceptable levels of maternal and fetal complications [33, 45].

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IMPROVEMENT THE PRO-HEALTH FUNCTIONALITY OF LENTIL SPROUTS BY FEEDING OF THE PHENYLPROPANOIDS PATHWAY

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ABSTRACT

Incorrect diet is one of the most important factor contributes to the synthesis of free radicals that are involved in most of pathological disorders and diseases. There are much evidence that the regular intake of legumes, phenolics-rich vegetables, reduces the risk of diet-related diseases such as obesity, diabetes, cardiovascular disease, hypertension and cancers. Germination has a positive effect on the profile of antioxidant compounds; however, their content is usually lower compared to the dormant seeds. The aim of the study was to investigate the impact of the phenylpropanoid pathway feeding on the phenolics content and antioxidant activity of lentil sprouts. Time of phenylalanine addition (watering in the 1st, 2nd and 3rd day of sprouting) and duration of its application (single or continuous) were optimized. Compared to control, all the studied variants improved phenolics content; however, the best results were found for the 4-day of sprouts obtained after the continuous addition of 1mM phenylalanine from 1st day of cultivation (68.78 mg/g d.m.) (mg per g of dry mass). A promising results were also obtained after continuous feeding. An increase of phenolics observed after phenylalanine addition was translated on the antioxidant capacity of sprouts. The highest ability to quench free radical was determined for the 2-day-old sprouts obtained from single and continuous supplementation with 1mM phenylalanine in the 1st day of cultivation - 7.51 mg TE- g d.m. and 7.81 mg TE g d.m., respectively. The highest reducing ability was found in the sprouts continuously fed from 3th day (an increase by about 10% in respect to the control).

BACKGROUND

Nowadays, consumers attach great importance to a healthy life style and properly balanced diet. Despite of nutritional value, natural/plant-based foods are a good source of nutrient, vitamins, minerals and polyphenols [1]. The regular intake of legumes, vegetables, fruits, nuts and fishes reduces the risk of diet related diseases such as obesity, diabetes, cardiovascular disease, hypertension and cancers that are caused by the consumption of highly processed products rich in saturated fatty acids, trans-fats, large amounts of salt and sugar. These products are usually high-calorie and they are poor in biologically active compounds such as antioxidants or vitamins [2]. However, in human body free radicals are produced in normal conditions, incorrect diet is one of the factors contributing oversynthesis of free radicals. Free radicals are an atoms, molecules or ions with unpaired electron, they are generated by our body by various endogenous systems [3]. They cause the formation of oxidative stress being the imbalance between reactive oxygen/nitrogen species (ROS/NOS) and the antioxidant defense system. As it is well-known that oxidative stress is involved in the most of pathological diseases. ROS/NOS can cause oxidation of lipids, proteins and DNA with following tissue damage. Toxic products of oxidation proceed cytostatic effects causing membrane damage and lead into cell death via apoptosis or necrosis [4]. Oxidative stress is involved in etiology of neurodegenerative diseases (Parkinson's and Alzheimer's disease) [5], metabolic diseases (diabetes, atherosclerosis, arthritis) [6], immunological diseases [7] and even cancer [8].

The balance status of the cell is maintained by antioxidant enzymes such as catalase, superoxide dismutase, glutathione S-transferase and other substances such as glutathione, vitamins A, C, E and phenolic compounds ROS [9], [4]. The level and activity of enzymatic components the antioxidant system is usually increased in many stresses. On the other and non-enzymatic antioxidants are usually introduced with diet. In this group a special place is booked for phenolics compound being plant secondary metabolites with documented nutraceutical properties [10].

Invaluable source of phenolic compounds is sprouted food e.g. mung beans, radish, broccoli, sunflower [1]. Such product are also characterized by an increased minerals content, dietary fiber, valuable protein, fatty acids omega-3. They also contain low calories (for example 100g of radish sprouts contain about 35 kcal), therefore are recommended to people who slim down. [11]. Sprouts are very popular, cheap, ready to eat and due to unique composition may be recognized as a new source of functional foods. It was confirmed that their consumption reduces risk of cancer, hypertension, diabetes and cardiovascular disease [12]. Germination has an positive effect on profile of antioxidant compounds as well. Compared to raw seeds, sprouts have stronger antioxidant properties mainly due to the higher content of polyphenols [13]. Phenolics in planta are mainly synthetized in the phenylpropanoid pathway, where tyrosine and phenylalanine are the precursor of phenolic acids. As a result of deamination, cinnamic acid and its hydroxy derivatives are formed [14]. Accumulation of phenolics in the sprouted food may be successfully increased by employing the elicitation and precursor feeding [15].

The aim of this study was to investigate the impact of phenylalanine feeding on the content of phenolic compounds and antioxidant activity of lentil sprouts.

MATERIAL AND METHODS

Chemicals

ABTS (2,2-diphenyl-1-picrylhydrazyl) was purchased from Sigma–Aldrich company (Poznan, Poland). All others chemicals were of analytical grade.

Materials

Lentil seeds var. Tina were purchased from PNOS S.A. in Ozarów Mazowiecki, Poland. Seeds were disinfected in 1% (v/v) sodium hypochloride for 10 min, then drained and washed with distilled water until they reached neutral pH. They were soaked 6 hours in distilled water and dark germinated for 5 days (ready-to-eat sprouts) in a growth chamber on Petri dishes (O 125 mm) lined with absorbent paper (approximately 150 seeds per dish). Seedlings were watered daily with 5 mL of Milli-Q water (C, control). For phenylalanine feeding sprouts were watered with 1 mM phenylanine. To define an optimal way for introduction of precursor single and continuous treatments were studied. Sprouts were sprayed in the 1st day of cultivation (S1) and then watered with water. Analogically, phenylalanine was also introduced in the 2nd (S2) and 3rd day of sprouting (S3). Sprouts was also consciously treated with precursor solution - starting from the 1st (C1), 2nd (C2) and 3rd (C3) day of cultivation.

Phenolic content and antioxidant activities

Extracts preparation

Lyophilized sprouts (0.2 g) were extracted three times with 4 mL of acetone/water/ hydrochloric acid (70:29:1, v/v/v). After centrifugation (10 min., 6800 x g) fractions were collected, combined and used for further analysis.

Phenolics analysis

The amount of total phenolics was determined using Folin-Ciocalteau reagent [16]. To 0.5 mL of the sample, 0.5 mL H2O, 2 mL Folin–Ciocalteau reagent (1:5 H2O) were added, and after 3 min, 10 mL of 10% Na2CO3 and the contents were mixed and allowed to stand for 30 min. Absorbance at 725 nm was measured. The amount of total phenolics was calculated as gallic acid equivalents (GAE) in mg per g of dry mass (d.m.).

Antioxidant activities

Antiradical activity (ABTS).

The experiments were carried out using an improved ABTS decolorization [17]. The ABTS radical cation (ABTS+·) was produced by reacting 7 mM stock solution of ABTS with 2.45 mM potassium persulphate (final concentration) and allowing the mixture to stand in the dark for at least 6 h at room temperature prior to use. The ABTS+· solution was diluted to an absorbance of 0.7 ± 0.05 at 734 nm (Lambda 40 UV-Vis spectrophotometer, Perkin Elmer). The affinity of test material to quench ABTS free radical was evaluated according to the

following equation: scavenging % = [(AC – AA) / AC)] × 100, where:

AC – absorbance of control,

AA – absorbance of sample

Free radical scavenging ability was expresses as Trolox equivalents in mg per g of dry mass (d.m.).

Reducing power (RP).

Reducing power was determined by the method of Oyaizu [18]. Analyzed sample (2.5 mL) was mixed with phosphate buffer (2.5 mL, 200 mM, pH 6.6) and potassium ferricyanide K3[Fe(CN6)] (2.5 mL, 1%). The mixture was incubated at 50 oC for 20 min. Reactions were stopped with 0.5 mL 10% TCA (trichloroacetic acid) and centrifuging for 10 min at 6500 x g. The upper layer of solution (2.5 mL) was mixed with distilled water (2.5 mL) and 0.5 mL of 0.1% FeCl3 and the absorbance was measured at 700 nm. Reducing power was expressed as Trolox equivalents in mg per g of dry mass (d.m.).

Statistical analysis

All experimental results were mean ± S.D. of three parallel experiments. Two-way analysis of variance (ANOVA and Tukey`s post-hoc test) was used to compare groups within different elicitors. p values < 0.05 were regarded

as a significant.

REASONS FOR OBESITY

Obesity is the result of a positive energy balance, whose formation is influenced by many factors: innate (genetic), environmental (acquired) and the hormonal state of the body.

Genetic variation.

We detect more than 360 genes that shape a predisposition to the development of obesity. However, so far not a single one has been identified as the principal gene or mutations which would be the direct cause of the development of obesity. Mutations can affect the genes governing the collection of food, adipocyte maturation and metabolism.

Monogenic obesity is rare and analyzing it, one can explore mechanisms, eg. the control of appetite, leptin gene and its receptor and the gene encoding another protein melanocortin pathway: proopiomelanocortin (POMC), proconvertase 1 (PC1) and proteins involved in the functioning of the neural network of the hypothalamus. At the moment, there are around 200 described, confirmed cases of monogenic conditioned obesity. Obesity determined by multiple genes, is of more clinical significance to understanding the mechanisms of obesity due to its higher prevalence. Polymorphism of multiple genes reflected in population regards propensity to accumulate excess body fat in a specific environment (i.e. "obesogenic" environment). Obesity is not the result of specific mutations or aberrations of chromosomes (as in the above-mentioned types of obesity), but is the result of polymorphisms - in the molecular sense and occurs in over 2% of the population differences in the DNA, which translate into a significant change in protein function [1]. Obesity is therefore determined by multiple genes.

In 1962, Neel introduced the hypothesis that explained the environmental non-specificity of obesity. He introduced the theory of the so-called "thrifty genotype" which helped man survive in times of famine, and thus natural selection favored individuals who stockpile energy in the form of fat. And although times have changed, genotypes with such properties have survived to modern times, as the human genome is not able to adapt to the modern diet [12].

Environmental variability.

The progress of civilization and economic lifestyle change appear to be responsible for the increasing prevalence of obesity epidemic in the last 25 years. The occurrence of two phenomena seems to be crucial. The first is the availability of high-caloric and processed foods (i.e. junk food high in fats and simple carbohydrates) and the second is a limitation of daily physical activity. In the last hundred years, the fat content (40-45% vs. 15-20%) has significantly increased in foods, and intake of complex carbohydrates, fiber and minerals [11] has decreased. In recent years, more and more attention is paid to the problem of diet-induced obesity which inhibits basic metabolism [1].

RESULTS AND DISCUSSION

Synthesis of phenolics (phenolics acids sand flavonoids) include the metabolism of phenylalanine, which is converted by an ammonia lyase into trans-cinnamic acid, followed by hydroxylation at the 4-position of the aromatic ring forming 4-hydroxycinnamic acid or p-coumaric acid [19]. The biosynthetic pathway reveals that tyrosine and phenylalanine may serve as precursors for phenylpropanoids synthesis [20].

The effect of pathway precursor feeding with phenylalanine on the total phenolics content in lentil sprouts is presented in Figure 1. The best results were found for the 4-day of sprouts obtained after the continuous addition of 1mM phenylalanine from 1st day of cultivation (68.78 mg/g d.m.) and also for the 5-day-old sprouts obtained after single addition of 1mM phenylalanine in the 3rd day of cultivation (67.88 mg/g d.m.). These results are compatible with those published by Christopoulos and Tsantili [21] who reported that changes in total phenolic compounds could be justified by the corresponding changes in PAL (Phenylalanine ammonia lyase) activity (for which the substrate is phenylalanine), confirming that an increase of phenolic was attributed, at least partially, to PAL activity. Świeca [22] reported that total phenolics content in buckwheat sprouts was significantly ($p < 0.05$) elevated by the feeding of seeds with tyrosine and shikimic acid and with further elicitation – an elevation by about 30% and 17% with respect to the control sprouts, respectively. Similar results were obtained by Edahiro, Nakamura, Seki, & Furusaki [23], who investigated the effect of repetitive feeding of strawberries with phenylalanine on anthocyanin accumulation and cell growth. They reported than the cultures fed with phenylalanine accumulated intracellularly anthocyanins regardless the way of application (the single and repetitive feeding).

The effect of pathway precursor feeding with 1mM phenylalanine on antioxidant capacity in lentil sprouts is

presented in Figure 2. The highest ability to quench free radical was determined for the 2-day-old sprouts obtained from single and continuous supplementation with 1mM phenylalanine in the 1st day of cultivation - 7.51 mg TE/ g d.m. and 7.81 mg TE/ g d.m., respectively (mg TE/ g d.m.- Trolox equivalents in mg per g of dry mass). The highest reducing power was found in the sprouts continuously fed from 3th day (an increase by about 10% in respect to the control) (Figure 3.). Antiradical ability and the ability to inhibit lipids peroxidation were also effectively improved in the buckwheat sprouts by feeding of seeds with shikimic acid, where compared to the control sprouts an elevation of about 14% was found [15]. Contrary to our results, feeding with methionine and tryptophan (precursors of aliphatic and indolic glucosinolates) did not result in any significant elevation of the glucosinolates content in broccoli sprouts [16]. On the other hand antioxidant activity of lentil sprouts was successfully improved by supplementation of seeds with shikimic acid, phenylalanine and tyrosine (combined with UV-B treatment) [24].

CONCLUSIONS

The antioxidant capacity of lentil sprouts may be successfully increased by phenylalanine feeding. The obtained sprouts were characterized by an increased content of phenolics, improved reducing power and antiradical activity. Most importantly, a final effect was dependent on the time of precursor application as well as duration of feeding.

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ABBREVIATIONS

Ac – absorbance of control sample
Aa – absorbance of sample
mg GAE/ g d. m – gallic acid equivalents in mg per g of dry mass
mg TE/ g d.m. – trolox equivalents in mg per g of dry mass
NOS – nitrogen oxide synthase
PAL – Phenylalanine ammonia lyase
ROS – reactive oxygen species

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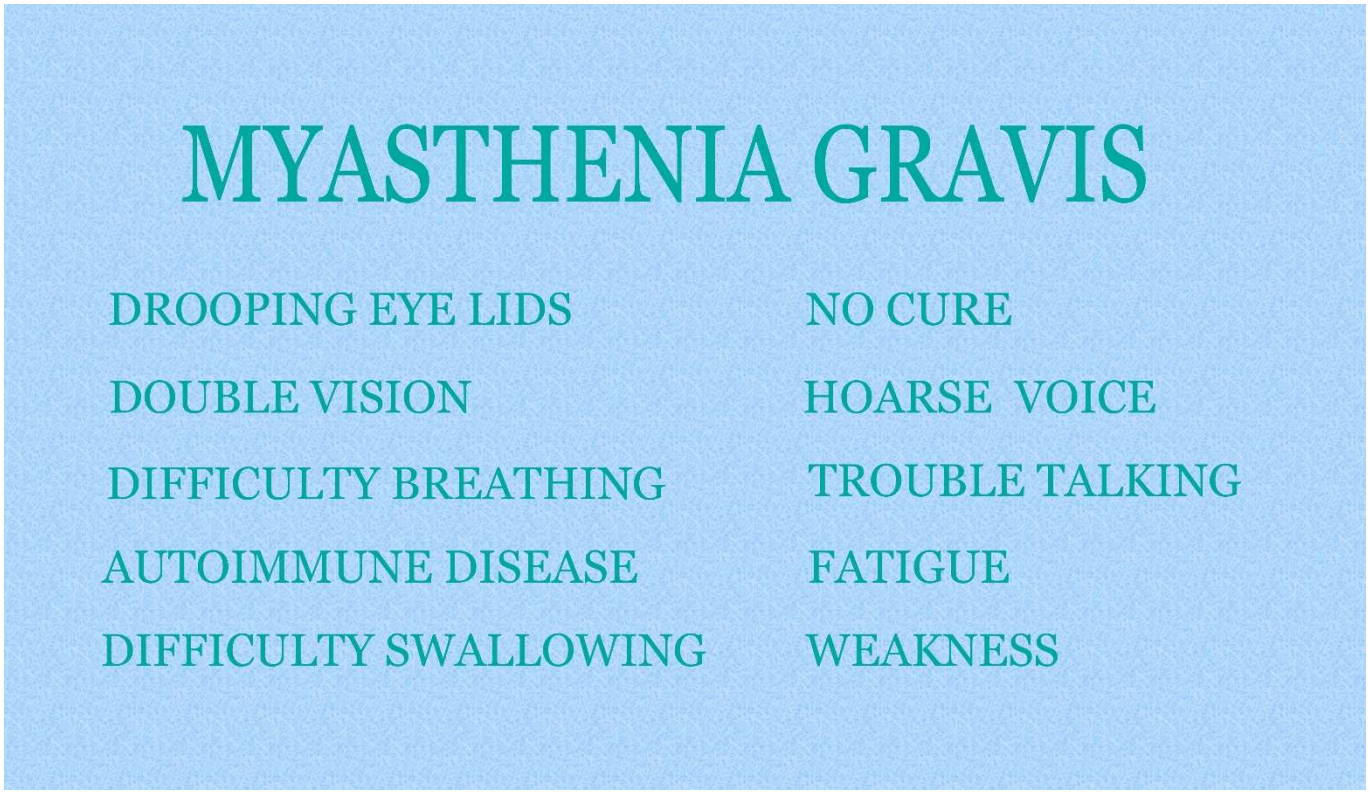

MYASTHENIA GRAVIS – CASE REPORT AND BRIEF REVIEW OF THE LITERATURE

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RUNNING TITLE	Myasthenia gravis
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ABSTRACT

Myasthenia gravis is a rare autoimmune neuromuscular junction disease. It is characterized by fluctuating skeletal muscle weakness, which worse during repetitive activities and improve with rest. There is a bimodal distribution to the age of onset with an early peak in the second and third decades of life in women and a late peak in the sixth to eighth decades in men. This paper described a case of a 57-year-old male patient, who was admitted to the Department of Neurology due to left eyelid drooping, left ear hearing loss, lower left mouth corner, speech and swallowing disorders, dizziness and memory impairment. These disorders have appeared about two weeks ago, intensified during the day and after exercise. In the interview, the patient informed about resection of mediastinal tumor - thymoma. Differential diagnosis included stroke, peripheral facial nerve injury, myasthenia gravis and myasthenic syndromes. Neuroimaging did not show any significant pathologies. In electromyography features of myogenic signal were observed. The titer of antibodies against the acetylcholine receptor was elevated. Based on clinical signs and diagnostic tests, myasthenia gravis was diagnosed. The patient, treated with pyridostigmine bromide, get an improvement in neurological status. In conclusion, diagnosis of myasthenia gravis in its early stages may cause diagnostic difficulties. In symptomatic treatment cholinesterase inhibitors and immunosuppressants are used. About 5% of patients die from myasthenic crisis. An important element of medical care is the education of the patients and their families.

BACKGROUND

Myasthenia gravis (MG) is the most common neuromuscular transmission disorder, which cause weakness of skeletal muscles during the exertion [1]. Muscles such as those that control eye, facial expression and neck and limb movements may be affected. The disease is characterized by the presence of circulating antibodies against components of the neuromuscular junction [2]. The name of this chronic neuromuscular disease means "grave, or serious muscle weakness" in Latin and Greek origin. The first to write about MG were Thomas Willis in 1672 and Samuel Wilks in 1877. In 1895, a German physician Friedrich Jolly proposed the term "myasthenia gravis pseudo-paralytica" [3]. Myasthenia gravis affects 70 to 320 persons per million [4, 5]. It is newly diagnosed in 3 to 30 per million people each year [6]. The sex and age of onset of the disease influence the course of disease. MG can occur at any age, but there tends to be a bimodal distribution to the age of onset with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance) [7]. Zieda and co-authors show a high prevalence and increasing incidence of late-onset MG [8]. A population-based case-control study found that women in the postpartum period had an increased risk for the clinical onset of MG [9]. Many researches have suggested an association of myasthenia gravis with other autoimmune diseases, including neuromyelitis optica, autoimmune thyroid disease, rheumatoid arthritis and systemic lupus erythematosus [1, 10]. The aim of the study is to present a case report of a patient admitted to the Department of Neurology at Medical University of Lublin due to a weakness of the eye muscles. During hospitalization, a series of diagnostic tests were performed, supporting myasthenia gravis diagnosis. The work is based in part on a review of the literature of the last 5 years of PubMed concerned myasthenia gravis.

CASE REPORT

A 57-year-old male patient was admitted to the Emergency Department due to eyelid drooping and excessive lacrimation of the left eye, hearing loss and tinnitus of the left ear and lower left corner position of the mouth. In addition, he suffered from speech and swallowing disorders, hypersensitivity to light, dizziness and memory impairment. These disorders have appeared about two weeks earlier, intensified during the day and after exercise. Similar symptoms appeared three and six months earlier, but they disappeared spontaneously. In the interview, the patient reported being treated for hypertension and type 2 diabetes for three years. He took telmisartan and metformin. A few months before admission to the hospital, he underwent surgical resection of the front mediastinal tumor. Histopathological result showed it was a tumor originating from the epithelial cells of the thymus, thymoma. The patient underwent a computed tomography (CT) scan of the head, in which no significant focal changes, no features of intracranial hemorrhage or edema, but only mediocre cortical atrophy of the brain were found.

The neurological examination revealed features of dysarthria, dysphagia, left eyelid ptosis, left-sided hearing loss, lower left mouth corner position, contracture of the third toe of the left upper limb and positive apokamnosis symptom in bulbar muscles. In order to further diagnosis, the patient was admitted to the Chair and Clinic of Neurology of Medical University in Lublin. During the hospitalization, head magnetic resonance (MR) examination was performed. This study revealed the presence of small, scattered focal lesions of vascular ischemia within the white matter of the frontal lobes and the partial lack of airiness of the pyramids of both temporal bones. After the administration of paramagnetic contrast medium, there were no signs of pathological enhancement in intracranial structures.

Due to a history of mediastinal surgery, a CT scan of the chest was performed, in which tissue structures that could correspond to adipose tissue and postoperative changes were visualized. A thoracic surgery consultation was planned in an outpatient setting to assess the radicality of tumor resection. Due to the left ear hearing loss reported by the patient, an audiogram, impedance and laryngological consultation were performed. It showed a small polyp of the left vocal cord. The patient was referred for planned treatment in the Otolaryngology Clinic. In the audiogram, the hearing impairment of the left ear was confirmed to approximately 80 dB.

In the neuromuscular transmission study, features of myogenic signal were observed. The result of the muscle fatigue test was abnormal - decreases in the initially reduced muscle response amplitude up to 68% (norm up to 10%) were noticed. The changes were intensified in proximal segments with a predominance in the bulbar muscles. The result of the EMG study indicated generalized post-synaptic dysfunction of the neuromuscular junction. The serologic tests for autoantibodies, both AChR and MuSK, were performed. The titer of antibodies against the acetylcholine receptor was elevated (49.0 nmol/l).

Based on clinical symptoms and additional diagnostic tests, the man was diagnosed with myasthenia gravis. Cholinesterase inhibitor Pyridostigmine was included in the treatment. Due to speech disorders, the patient was covered by speech therapy in the Clinic. The patient was discharged home in a good general condition, get an improvement in neurological status. Daily blood pressure control and press diary management, diabetic and low-cholesterol diet, regular medicines taking and control it the Neurological and Thoracic Outpatient Clinic were recommended. After two months' therapy, the presented patient is still complaining about fatigable chewing and sporadic swallowing disorders. However, these symptoms are much less expressed thanks to anticholinesterase treatment.

DISCUSSION

The differential diagnostic considerations early in the presentation of myasthenia gravis, depending on the initial symptoms may cause some difficulties, as the symptoms can be subtle and hard to distinguish from both normal variants and other neurological disorders. There are a number of neuromuscular disorders that can

be confused with myasthenia clinically [10]. This should always be kept in mind so that a careful history, physical examination, and laboratory testing can allow the correct diagnosis to be established. The differential diagnosis of MG includes conditions that mimic ocular myasthenia like thyroid ophthalmopathy, chronic progressive external ophthalmoplegia (CPEO) or Kearns-Sayre syndrome (KSS), myotonic dystrophy and oculopharyngeal muscular dystrophy and brainstem and motor cranial nerve pathology [11]. The differential also includes conditions that mimic generalized myasthenia: generalized fatigue, motor neuron disease (amyotrophic lateral sclerosis, ALS), Lambert-Eaton myasthenic syndrome (LEMS), the Miller Fisher and pharyngeal-cervical-brachial variants of Guillain-Barré syndrome, botulism and congenital myasthenic syndromes [1, 11, 12]. The LEMS shares with MG the involvement of the neuromuscular junction, and it has a similar autoimmune pathophysiology. Involvement of the bulbar muscles or diplopia is less common in LEMS than in MG, but ptosis is frequently seen [12, 21]. The early differential diagnosis should also include stroke and peripheral facial nerve injury, especially when there are symptoms such as eyelid ptosis, lower mouth corner position and speech disorders, like in the presented patient. CT scan of the head can help to exclude focal changes, features of intracranial hemorrhage or edema. Structural disease of the brainstem can cause isolated ocular symptoms. As examples, parasellar tumors and aneurysms can impair function of the third, fourth, and sixth cranial nerves, leading to symptoms similar to ocular myasthenia. For patients with ocular or bulbar symptoms, an MRI of the brain is appropriate to exclude these disorders. CT scanning or ultrasonography of the orbits is helpful in the differential diagnosis of ocular myasthenia and thyroid ophthalmopathy. In cases of possible multiple cranial nerve abnormalities, examination of the cerebrospinal fluid for abnormal cells and cytology is usually necessary [11, 12]. Electrodiagnostic studies are particularly crucial in the differential diagnosis of other neuromuscular disorders [1, 10].

The course of myasthenia gravis is variable. We can observe different symptoms and signs, which change due to for example infection or pregnancy [1]. The hallmark of the disorder is a fluctuating degree and variable combination of muscular weakness. There are two main clinical forms of MG: ocular and generalized [12]. In ocular myasthenia, the weakness is limited to the eyelids and extraocular muscles, while in generalized disease, the weakness commonly affects ocular muscles, but also involves a variable combination of bulbar, limb, and respiratory muscles [12, 13]. Patients who have detectable antibodies to the acetylcholine receptor (AChR) or to the muscle-specific receptor tyrosine kinase (MuSK) are considered to have seropositive myasthenia gravis, while those lacking both AChR and MuSK antibodies on standard assays are considered to have seronegative myasthenia [13]. About half of patients with purely ocular myasthenia are seropositive, compared with approximately 90 percent of those with generalized disease [12, 14]. We notice that 8-10% of patients are positive for anti-MuSK antobodies [14]. The presented patient had elevated titer of antibodies to the acetylcholine receptor (AChR) up to 49.0 nmol/l.

The cardinal feature of myasthenia gravis is fluctuating skeletal muscle weakness, often with true muscle fatigue. The fatigue is manifested by worsening contractile force of the muscle. The weakness may fluctuate throughout the day, it is most commonly worse with repetitive activities and improve with rest. Moreover weakness is worsened by exposure to heat, infection, and stress [1, 11]. More than 50% of patients present with ocular symptoms of ptosis and/or diplopia [3]. Of those who present with ocular manifestations, about half will develop generalized disease within two years [3, 10]. The ptosis may start unilaterally and then become bilateral or be bilaterally from the beginning. At times, it may be so severe as to occlude vision. The pupils are always spared in myasthenia gravis, helping in the differentiation from other disorders [11]. About 15% of patients, like the described one, present with bulbar symptoms. These include dysarthria, dysphagia, and fatigable chewing [10, 15]. Less common presentations include isolated neck weakness, isolated respiratory muscle weakness, and distal limb weakness.

The thymus gland could play a role in myasthenia gravis, but its function is not fully understood. The thymus gland is a gland that controls immune function. In AChR antibody-positive MG, more than 75 percent of patients have thymic abnormalities. In those with thymic pathology, thymic hyperplasia is most common (85 percent). Up to 15 percent of person with myasthenia gravis have a tumor in their thymus gland [16]. So, it was in the presented case. The patient underwent surgical resection of the front mediastinal tumor a few months before admission to the hospital. Histopathological result showed it was a thymoma. That fact was also helpful in differential diagnosis, indicating MG as an often concomitant disease. The thymic tumors are usually noninvasive cortical thymomas, but invasive thymic carcinoma can occur. Considering the low sensitivity and specificity of serological testing, computerized tomography (CT) or MR imaging studies are mandatory to rule out the presence of a thymoma [10, 16]. Surgical treatment is strongly recommended for patients with thymoma [11]. Thymectomy may not be a viable therapeutic approach for anti-MuSK antibody-positive patients because their thymi lack the germinal centers and infiltrates of lymphocytes that characterize thymi in patients who have anti-AChR antibodies. Most experts consider thymectomy to be a therapeutic option in anti-AChR antibody-positive generalized MG with disease onset before the age of 50 years [11]. Thymic lymphoid hyperplasia and severe symptoms may negatively affect prognosis of the disease following thymectomy [17]. Moreover, during thymectomy, the unpredictable response to muscle relaxants and volatile anesthetic agents could provoke muscle weakness. It could be also the cause of postoperative myasthenic crisis [18]. Choi Decroos and co-authors show the detection of striational antibodies in early-onset MG may be helpful in predicting the presence of thymoma. The negative predictive value of thymoma in the absence of acetylcholine antibodies is more than 99 percent [19].

The diagnostics of myasthenia gravis is mainly based on interview, on physical and neurological examination, blood test and electrophysiological features [15, 16]. Bedside tests, which include the Edrophonium Chloride test and the ice pack test are easy to perform and sensitive, but they have major limitations due to concerns about excess false-positive results with these techniques [16]. More reliable laboratory methods that aid in the confirmation are serologic tests for autoantibodies and electrophysiological studies (repetitive nerve stimulation studies and single-fiber EMG). For measure the nerve's ability to send a signal to muscle, repetitive nerve stimulation (RNS) is a valuable diagnostic method for this disease [20]. The diagnostic sensitivity of these studies also varies considerably depending on whether the patient has ocular or generalized disease. In generalized myasthenia gravis, the diagnostic sensitivity of RNS studies is approximately 75 to 80 percent, while that of single-fiber electromyography (SFEMG) is approximately 95 percent [21]. An RNS study is considered positive (abnormal) if the decrement in response is greater than 10 percent. To maximize the sensitivity, the muscles tested should be warm, and acetylcholinesterase inhibitors should be held for 12 hours before the study [22]. In the presented case an amplitude with the first four to five stimuli was 68%.

A precise diagnosis play a significant role in order to choose right treatment. Management should be individualized according to patient characteristics and the severity of the disease. In the presented patient, thanks to hospitalization, differential diagnosis was quickly performed and the proper treatment was early initiated. There are four basic therapies used to relieve symptoms of MG: symptomatic treatment with cholinesterase inhibitors, rapid short-term immunomodulating treatment with plasmapheresis and intravenous immunoglobulin, chronic long-term immunomodulating treatment with glucocorticoids and other immunosuppressive drugs and surgical treatment (thymectomy).

The initial therapy for most patients with myasthenia gravis is an oral acetylcholinesterase inhibitor (also called anticholinesterase medication). Pyridostigmine bromide is the main cholinesterase inhibitor currently in use [23]. It has a rapid onset of action, about 15 to 30 minutes, with peak action at about two hours, and its effects last for three to four hours. It is necessary to take these drugs regularly, every four to six hours during the day, to maintain symptomatic benefit [13, 23]. Acetylcholinesterase inhibitors are the first line of treatment due to their safety and ease of use. These drugs retard the degradation of acetylcholine (ACh) that occurs by enzymatic hydrolysis in the neuromuscular junction [22, 24]. They provide marked improvement in some patients and little or none in others. In general, limb and bulbar symptoms (dysphagia, dysarthria, fatigable chewing) respond better to anticholinesterase drugs than the ocular manifestations (ptosis and diplopia) [23]. Acetylcholinesterase inhibitors provide only symptomatic therapy and are usually not sufficient in generalized MG. In the presented case, after two months' anticholinesterase therapy, symptoms such as fatigable chewing and sporadic swallowing disorders are still observed, but much less expressed.

The second therapeutic modality in MG is the administration of immunomodulating agents. Corticosteroids or immunosuppressive therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine [25]. Commonly used immunotherapeutic drugs in MG are prednisone, azathioprine, methotrexate, mycophenolate mofetil (MMF), cyclosporine and tacrolimus [1, 13, 25]. Even when immunotherapeutic drugs are used, it is common to continue the use of anticholinesterase medications in order to reduce the dosage of immunosuppressive drugs and therefore minimize their adverse effects [13]. The onset of glucocorticoids administration benefit generally begins within two to three weeks. Many myasthenic patients require long-term immunosuppressive therapy [10]. Azathioprine still remains the first choice [10]. A significant disadvantage of azathioprine is the delayed onset of action. It becomes apparent 6–12 months after commencement. Commonly, azathioprine is therefore started combined with prednisolone to achieve a rapid therapeutic effect [10]. MMF appears to be more potent and acts faster than azathioprine [24].

Plasmapheresis and intravenous immunoglobulin (IVIG) are rapid immunotherapies that work quickly but have a short duration of action. Plasmapheresis (plasma exchange) directly removes acetylcholine receptor antibodies from the circulation. Clinical improvement with plasmapheresis roughly correlates with the reduction in antibody levels [26]. A typical course of treatment consists of five exchanges, from 2 to 4 liters each one, over 7 to 14 days [10]. The beneficial clinical effect of plasmapheresis is usually seen within days, but the benefit typically lasts only three to six weeks. The mechanism of action for IVIG in MG is uncertain. As with plasmapheresis, the effect of IVIG is seen typically in less than a week, and the benefit can last for three to six weeks [26]. A significant disadvantage of these rapid immunotherapies is high cost. They are usually reserved for certain situations, such as myasthenic crisis, preoperatively before thymectomy or other surgery, as a "bridge" while initiating slower acting immunotherapies, or as an adjuvant to other immunotherapeutic medications in patients with refractory MG [23, 27]. Refractory MG is defined as a disease that is "unchanged or worse after corticosteroids and at least two other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician" [14, 25]. Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to the immunosuppressive agents, the following therapies may also be used in refractory MG: chronic IVIG and chronic plasma exchange, cyclophosphamide or Rituximab, for which evidence of efficacy is building [24, 25, 28]. Rituximab is a chimeric IgG monoclonal anti-CD20 antibody that depletes B cells [24]. Its original role was in the treatment of non-Hodgkin's lymphoma but it has now been shown to be effective in treating refractory myasthenia gravis with or without thymoma and also MuSK antibody positive myasthenia gravis [10, 24]. Rituximab may work partly by modifying antigen

presentation by B cells, as well as reducing the number of antibody-producing plasma cells [29]. The most popular treatment regimen is that of 4-weekly 375 mg/m2 [10, 24].

Alternative treatments continue to be explored. Bortezomib is a proteasome inhibitor approved for treating patients with multiple myeloma. Recent preclinical studies in cell cultures and animal models, and clinical studies in organ-transplant recipients, have demonstrated that bortezomib can kill nonneoplastic plasma cells within hours [30]. In an experimental rat model for MG it could be shown that bortezomib leads to reduced acetylcholine receptor-antibody secretion, prevention of motor endplate damage and clinical improvement. This suggests that proteasome inhibitors could also be used for rapidly reducing autoantibody production in MG [30]. Schneider-Gold and co-authors describe rapid improvement in MuSK-antibody positive MG patient [31].

Belimumab is a human monoclonal antibody that inhibits B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS). Belimumab is already approved in the United States, Canada and Europe for treatment of systemic lupus erythematosus (SLE). BAFF is a potent B cell survival factor, and plays an essential role in B cell homeostasis and B cell function in the periphery. BAFF levels are increased in the circulation of MG patients [10]. That is why belimumab may well provide new treatment options for MG.

Eculizumab is a humanized monoclonal antibody functioning as a terminal complement inhibitor. Complement activation at the neuromuscular junction may be the primary cause of acetylcholine receptor loss and failure of neuromuscular transmission seen in MG [10, 32]. Eculizumab blocks the formation of terminal complement complex by selectively preventing the enzymatic cleavage of C5. It is the first therapy approved for the treatment of paroxysmal nocturnal haemoglobinuria. The primary analysis of the results of a phase 3, randomised, double-blind, placebo-controlled, multicentre study REGAIN on the use of eculizumab in severe and refractory generalized MG showed no significant difference between eculizumab and placebo. Eculizumab was well tolerated. However, the use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result and further research into the role of complement is needed [32].

With optimal treatment, the prognosis is good in terms of daily functions, quality of life and survival in the majority of patients suffering from MG [10].

CONCLUSION

It is essential to make a good diagnostic and have a good clinical workout to exclude other alternative diagnoses. A precise diagnosis play a significant role in order to choose right treatment. A good diagnosis is important for predict the course of disease. Using the spectrum of treatment options available nowadays, myasthenic symptoms could be controlled and the majority of patients can have a relatively high quality of life. Most patients have a good prognosis, but some are refractory to immunosuppressive treatment [2]. They suffer from recurrent myasthenic crises, a medical emergency that occurs when the muscle that control breathing weaken require intubation and mechanical ventilation [2, 33]. 15 to 20% of patients with MG are affected by myasthenic crisis at least once in their lives [33].

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ABBREVIATIONS

ACh – acetylcholine
AChR – acetylcholine receptor
ALS – amyotrophic lateral sclerosis
BAFF – B-cell activating factor
BLyS – B-lymphocyte stimulator
CPEO – chronic progressive external ophthalmoplegia
CT – computed tomography
dB – decibel
EMG – Electromyography
IVIG – intravenous immunoglobulin
KSS – Kearns-Sayre syndrome
LEMS – Lambert-Eaton myasthenic syndrome
MG – Myasthenia gravis
MMF – mycophenolate mofetil
MR – magnetic resonance
MuSK – muscle-specific kinase
RNS – repetitive nerve stimulation
SFEMG – single-fiber electromyography

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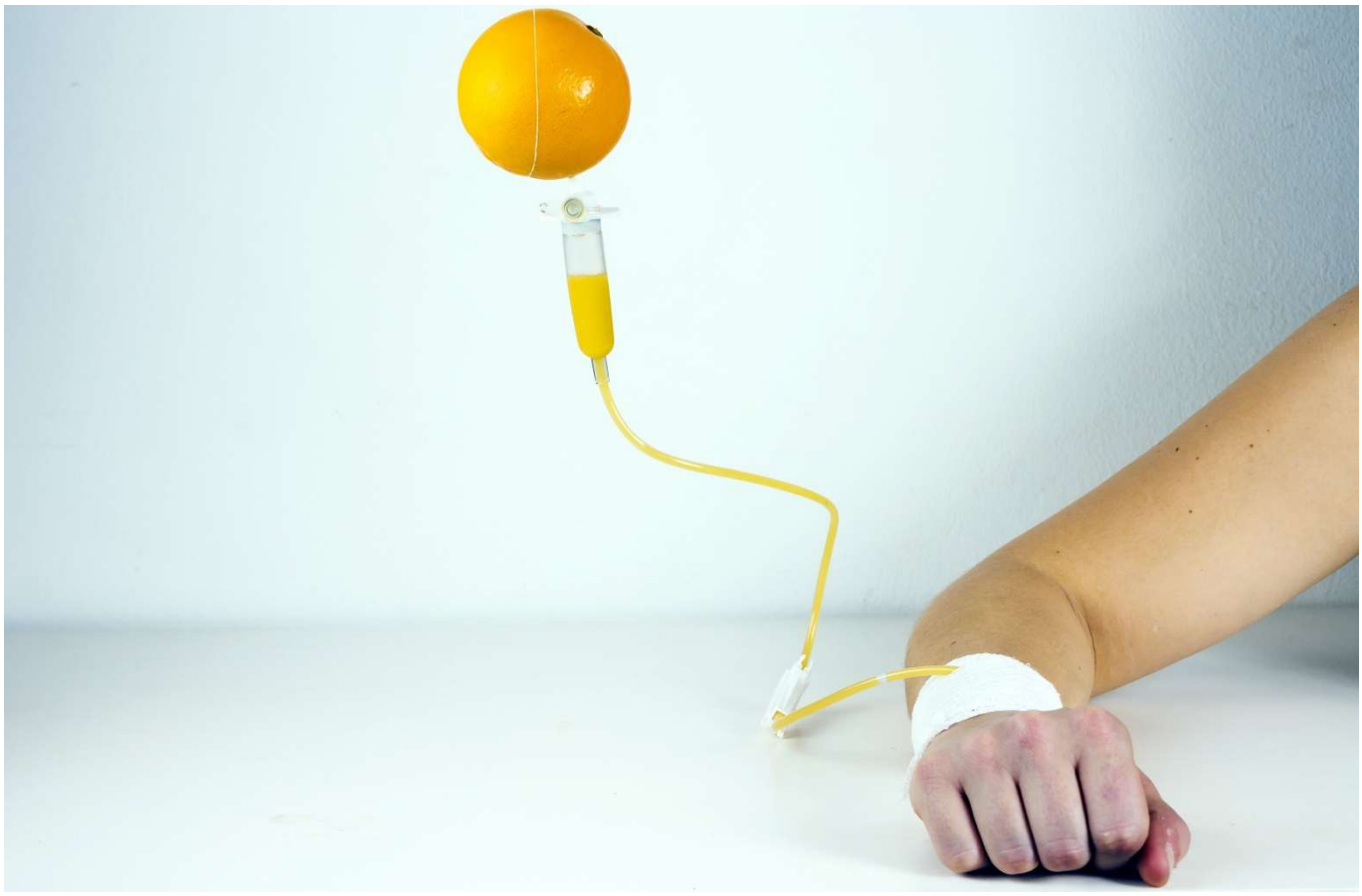

PREOPERATIVE IMMUNONUTRITION IN GASTROINTESTINAL CANCER PATIENTS

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CONFLICT OF INTERESTS	no conflicts of interest

ABSTRACT

Surgical procedures due to gastrointestinal tumors are associated with increased risk of postoperative complications and mortality. This is a result of malnutrition and impairment of the immune system. Using nutritional treatment containing immunomodulatory components before surgery may improve the nutritional status of patients and also the immune system by stimulating the host`s immune response, improving the nitrogen balance and controlling the inflammatory response. The nutrients with immunomodulatory effect include: arginine, glutamine, ω-3 fatty acids, and nucleotides. Despite many clinical research the role of preoperative immunonutrition remains unambiguous. The optimal dose of using it is also unknown. The aim of this study was analysis of the impact of preoperative immunonutrition on postoperative complications in patients with gastrointestinal cancer treated surgically. The authors reviewed the literature of effect of preoperative immunonutrition on postoperative complications, mortality, and length of stay in hospital in gastrointestinal cancer patients. The studies including immunonutrients such as arginine, glutamine, ω-3 fatty acids and RNA (ribonucleic acid) were reviewed. Preoperative immunonutrition seems to be effective in the prevention of postoperative complications, both infectious and noninfectious, as well reduction of mortality and shorter length of stay in hospital. Patients with malnutrition are definitely benefit of this kind of support. Further studies are needed to assess the effect of preoperative immunonutrition in patients treated surgically due to gastrointestinal cancer.

BACKGROUND

Gastrointestinal cancer surgery is associated with higher postoperative infections, non-infective complications and mortality. It is a result of impairment immune function, perioperative stress and malnutrition in these patients. Malnutrition is common problem in preoperative gastrointestinal cancer patients. It is estimated in 65 – 85% patients with upper gastrointestinal cancer [1-3].

MALNUTRITION IN GASTROINTESTINAL CANCER PATIENTS

Nutritional status can be assessed by several methods both in the form and biochemical test. The most commonly and the simplest approach of assessing the nutritional status of patients in hospital is SGA (Subjective Global Assessment). It allows identification of patients at risk of malnutrition [4-6]. Another regularly used form is screening form for assessing the risk of malnutrition NRS 2002 (Nutritional Risk Screening). The occurrence of risk of malnutrition in patient with gastrointestinal cancer may be determined when one of the following criteria is found:

- Weight loss > 10% over the last 6 months
- BMI (body mass index) < 18.5 kg /m^2
- Grade C on the SGA scale or result > 3 on the NRS 2002 scale
- Decreased plasma albumin level < 3 g/dl (excluding liver and kidney disease [7].

In patients over the age 65, the diagnosis of malnutrition that requires nutritional intervention is diagnosed at BMI <24 kg/m^2 and when unintentional weight loss is > 5% in the last 6 months [8].

Unintentional weight loss is observed in 31 – 87 % of patients. The range of weight loss depends on the type of tumor location. Unintentional weight loss > 10% in the last 6 months is reported by approximately 15 % of patients with gastrointestinal cancer. Malnutrition is observed in up to 80% of patients with advanced stage of cancer [2, 3]. An extremely important issue is the co-occurrence of impairment of the immune system. There is a disturbance of the basic functions for example the defensive range, support of regenerative process or active tolerance. Malnutrition additionally affects the impairment of the immune system in proportion to its severity. One of the symptoms of failure of the immune system is a decrease in the number of lymphocytes [9, 10].

IMMUNONUTRITION

One way to remedy this situation is to improve the work of patient`s immune system by supplementing the nutrient deficiencies necessary for the proper functioning of the body. Thanks to this, conditions will be created for the progressive restoration of the immunocompetent cells` efficiency. Participation in this is taken by nutrients that have ability to stimulate the host`s immune responses, improve the nitrogen balance and control of the inflammatory response. They also increase protein synthesis after surgery. These components include arginine, glutamine, ω-3 fatty acids, nucleotides (RNA) [11].

Arginine – it is consumed during the synthesis of proteins. It is essential substrate in many metabolic cycles. Deficiencies are observed in major injuries and cachexia. A beneficial effect on wound healing was observed [12]. Arginine administered orally or intravenously affects the immune system by stimulating the thymus to produce T lymphocytes and improving their efficiency, stimulating the function of macrophages, LAK cells (lymphokine-activated killer), NK cells (natural killer), allowing granulocytes phagocytosis. It also stimulates cancer cytotoxicity and has a protective effect during chemotherapy [13, 14].

Glutamine – it is the main source of nitrogen in the human body. It is particularly used by rapidly dividing cells. Glutamine administers to people with cancer appears to provide normal function of immune cells and intestinal epithelium.

Polyunsaturated fatty acids ω-3 –in the human body they are present in phospholipids of cell membranes. They affect the process of cell growth and differentiation as well as participate in inflammatory and immunological processes. ω-3 fatty acids reduce the inflammatory reaction while ω-6 fatty acids have a strong proinflammatory effect.

Nucleotides – it is suggested that nucleotide supplementation has a beneficial effect on the regeneration of intestinal villi as well as improves immune function [9, 12]

The level of immunonutrients is compensated very slowly therefore the measurable benefits of immunizing are visible after the necessary time. In case of omitting this phase, it may be unexpected deterioration of patient's condition [15-18]. Unfortunately, the legitimacy of preoperative immunonutrition in gastrointestinal cancer patients is unclear. The optimal duration of it is also unknown. According to current ESPEN (The European Society for Clinical Nutrition and Metabolism) guidelines, nutritional treatment containing immunologically active compounds should be used within 10-14 days in patients with cancer [20].

MATERIAL AND METHODS

The authors reviewed the literature of effect of preoperative immunonutrition on postoperative complications, mortality, and length of stay in hospital in gastrointestinal cancer patients. The studies including immunonutrients such as arginine, glutamine, ω-3 fatty acids and RNA were reviewed.

THE IMPACT OF PREOPERATIVE IMMUNONUTRITION ON POSTOPERATIVE OUTCOMES IN GASTROINTESTINAL CANCER PATIENTS

Hennesey et al. conducted a study on 524 patients undergoing surgical treatment of the gastrointestinal tract. The albumin level was tested preoperatively. Patients with postoperative complications had hypoalbuminemia before surgery. The reduced pre-

operative albumin level also correlated positively with the length of stay in hospital after surgery [21].

In Albania there was a study carried out among 694 patients prepared for surgery due to gastrointestinal cancer admitted to the surgical ward and treated in ICU (Intensive Care Unit). The patients were divided into two groups – well-nourished and malnourished. Preoperative malnutrition was found in 65.3% of all patients including 84.9% of patients with malignant neoplasms of gastrointestinal tract. Patients were not received preoperative immunonutrition as it is recommended. Malnutrition is a significant problem in surgical patients, especially in patients with gastrointestinal tumor. This study point out that insufficient preoperative nutritional support is associated with an increased incidence of infections, postoperative complications, mortality and longer ICU stay [1].

Xu and co examined 60 patients with gastrointestinal cancer. Half of them received preoperative immunonutrition in form of IMPACT for 7 days before the operation. After the surgical treatment, it was noticed that in the group of patients receiving immunotherapy, the percentage of postoperative complications was significantly lower. Moreover there was a relevant reduction in length of hospital stay after surgery in this group. After analyzing the results, the authors found that enteral preoperative immunonutrition improves the nutritional status and immune response in patients with gastrointestinal cancer. It also reduces the incidence of postoperative infections and complications in these patients [22].

In Japan there was a study made up of 55 esophageal cancer patients before surgical treatment. Twenty six of them received preoperative immunonutrition treatment in form of an industrial product IMPACT for 5 days preoperatively in an amount of 750 ml per day. Control group consisted of 29 patients. Definitely less patients [4/26] from group receiving preoperative immunonutrition experienced postoperative complications compared to the group without immunonutrition [10/29]. In this group of patients no postoperative deaths were observed, as well as their length of stay in hospital was lower than patients from control group. The average 6-month survival was relatively higher in patients from group with preoperative immunonutrition (92%) than in group without receiving immunonutrition (72%). Preoperatively immunonutrition significantly improved the results of surgical treatment. The supply of immunostymulatory nutritional treatment before esophageal cancer surgery appears to be right strategy for reducing infectious complications, mortality and length of stay as well as short-term survival [23].

Nakamura et al. conducted a study in esophageal cancer patients assessing the optimal amount of preoperative immunonutrition. Patients were divided into two groups, one of them consumed 500 ml of industrial immunonutrition IMPACT while second group were fed with 1000 ml of the product. Patients consuming a larger amount of immunonutrition developed diarrhea and loss of appetite. The study suggests that 500 ml dose of IMPACT is optimal for patients with esophageal cancer [24].

Fujitani et al. examined 244 well-nourished patients with early gastric cancer before complete gastrectomy. Patients were divided into two groups, first group was fed by immunostimulating substances 5 days before surgery while the second group was control. In group of patients received immunonutrition there was no reduction in the incidence of postoperative complications. Five-day preoperative immunonutrition did not protect well-nourished patients from postoperative complications [25].

Fukuda and co. carried out research among 800 patients with gastric cancer before surgical treatment. The risk of malnutrition was determined by means of unintentional weight loss > 10% within 6 months, BMI < 18.5 kg/m^2, grade C on the SGA scale, reduced level of albumin < 3.0 g/dl. Patients were divided into 4 groups: I Group – didn`t received preoperative immunonutrition, groups II, III, IV were fed respectively 1-9, 10-13 and ≥ 14 days. Adequate nutrition was assessed as an intake of > 25 kcal/kg/day. In 19 % patients malnutrition was observed. Postoperative complications were significantly higher in malnutrition patients. Patients with malnutrition, but fed adequately had less postoperative complications than malnourished patients without nutritional support or with duration < 10 days. Based on the study authors concluded that proper preoperative nutrition support reduces the occurrence of postoperative complications in malnourished patients with gastric cancer after surgery [26].

The study involved 67 patients with colorectal cancer without malnutrition before planned surgery. Patients were divided into two groups- first group (n=33) were fed with preoperative immunonutrition within 5 days before the operation. Second group was made up of patients without any nutritional treatment. In patients receiving nutritional support no postoperative complications were noticed. Preoperative enteral immunonutrition may be effective in the prevention of postoperative complications in patients with colorectal cancer without malnutrition [27].

In Switzerland, a prospective, randomized, double-blind, placebo-controlled were conducted in patients with gastrointestinal cancer before surgery. Only well-nourished patients were include in the study. Patients received preoperative immunonutrition in form of IMPACT or placebo. Nutritional treatment was used for 3 days before planned surgery. There was no significant improvement in the incidence of postoperative complications and infectivity between two groups. There was also no relevant difference in perioperative mortality and length of stay in hospital. Preoperative immunonutrition applied 3 days before planned surgery in well-nourished patients did not affect the improvement of postoperative complications [28].

CONCLUSIONS

To sum up there are more and more studies suggesting the appropriateness of preoperative immunonutrition nowadays. It seems to be effective in the prevention of as well postoperative complications, both infectious and noninfectious, reduction of mortality as length of stay in hospital. The patients diagnosed with malnutrition before planned surgical treatment can definitely benefit from

such nutritional support. Unfortunately, despite the suggestions, the optimal time of using immunonutrition is not determined. Further studies are needed to confirm the appropriateness of preoperative immunonutrition in patients with gastrointestinal cancer.

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ABBREVIATIONS

BMI – body mass index
ESPEN – The European Society for Clinical Nutrition and Metabolism
ICU – Intensive Care Unit
LAK – lymphokine-activated killer
NK – natural killers
NRS – Nutritional Risk Screening
RNA – ribonucleic acid
SGA – Sublective Global Assessment

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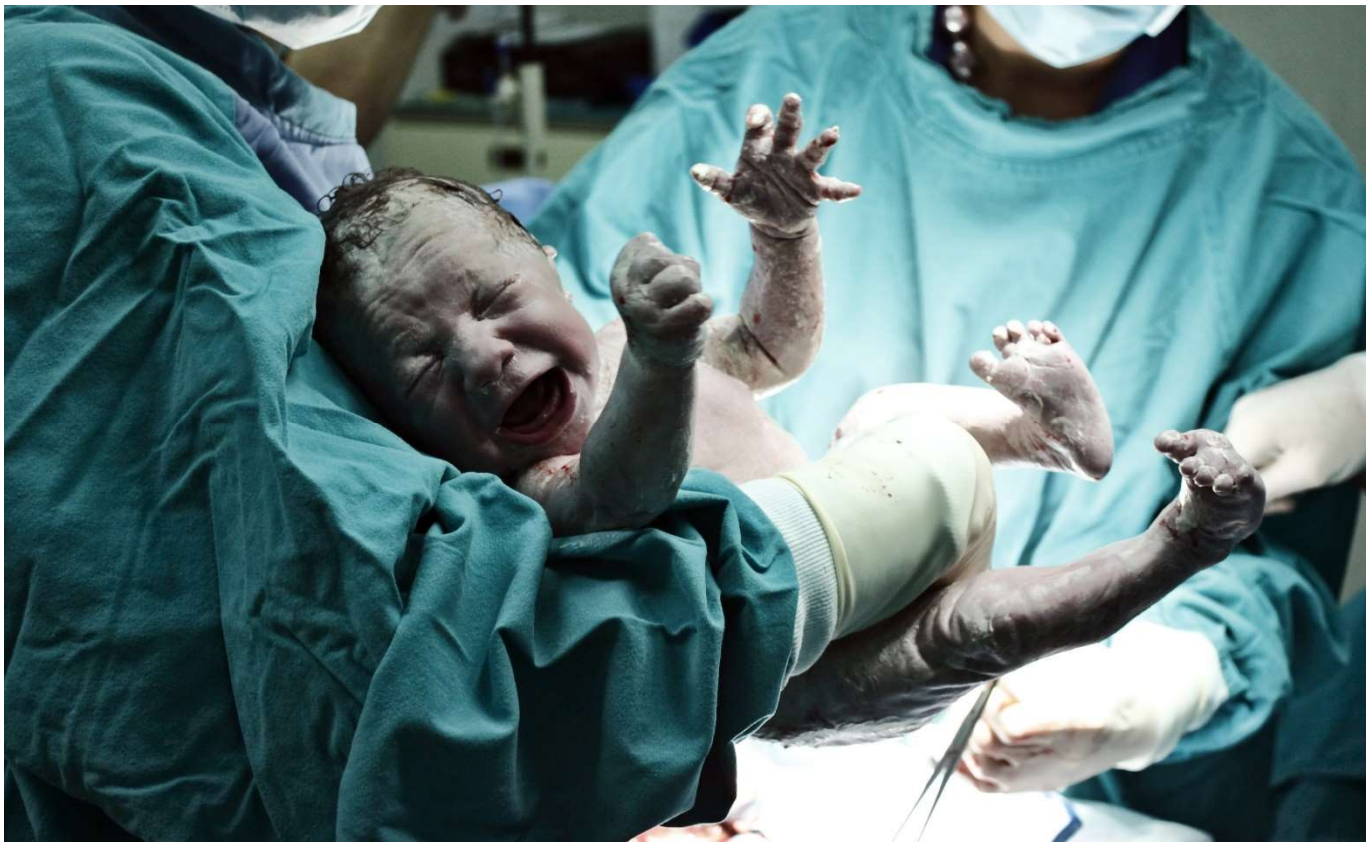

FETAL SKULL DEFECTS – THE BEST METHOD OF DELIVERY

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ABSTRACT

Neural tube defects (NTDs) are birth defects of the central nervous system that originate during embryonic development when the neural tube fails to close completely. They are the second most frequent category of congenital anomalies, after congenital heart disease. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. Recent developments in medicine have improved prenatal diagnosis, so that NTDs are diagnosed earlier and the diagnosis is more certain. In Poland, many fetuses with neural tube defects will continue to be delivered, as termination is unacceptable to many. As such, the question to be asked is the following– what is the best method of delivery in these situations. In our study, we analysed courses of pregnancies and methods of delivery of children with NTDs and we compared them with data from literature. The study was conducted in patients from the II Department of Obstetrics and Gynaecology, Medical University in Warsaw, Poland. The purpose of this analysis was to evaluate the advantages and disadvantages of vaginal deliveries compares to C- section. All analysed cases from our Department ended up with vaginal delivery. Careful analysis of these case reports and available literature, suggested, that there are no significant contraindications to vaginal birth for the pregnancies complicated by NTDs. Vaginal delivery of children with lethal defects is save and beneficial for the mother. It has less negative consequences for the women and her future reproduction health.

BACKGROUND

Neural tube defects (NTDs) are relatively common congenital anomalies that develop when a portion of the neural tube fails to close normally during the third and fourth weeks after conception. The resulting defect may involve the vertebrae, spinal cord, cranium or brain. Examples of NTDs are spina bifida (50%), anencephaly (40%), encephaloceles (8.5%), iniencephaly, spina bifida occulta (1.5%), ventriculomegaly, agenesis of the corpus callosum, microcephaly, Dandy–Walker syndrome and acrania [1]. It is difficult to estimate how many pregnancies with NTDs end with miscarriage, because many women do not know that they were pregnant. Infants that are alive at birth generally die within hours, but occasionally survive for a few days or weeks [2].

NTDs are multifactorial, with contributions from both genetic and environmental factors. The genetic basis is not yet well understood, but several nongenetic risk factors have been identified as have possibilities for prevention. These are gestational diabetes mellitus, lack of folic acid supplementation, antiepileptic drugs use during pregnancy, familial marriage, maternal obesity and advanced age of the mother. Rare risk factors include epigenetic modifications, maternal antibodies against folic acid's receptors and in vitro fertilisation [1, 3].

Tests for NTDs include ultrasound examination (95% effectiveness) and measurement of maternal serum alpha-fetoprotein (MSAFP), human chorionic gonadotrophin (hCG) and estriol. The diagnosis is confirmed with use of other tests, such as fetus' MRI in 23-32 Hbd, amniocentesis and concentration of cell-free placental DNA in maternal plasma [4]. Because NTDs are known to appear with other genetic disorders the karyotype should be also tested [1]. This examination helps to make diagnosis and estimate the prognosis.

Prenatal ultrasound screening is the first choice in diagnosing NTDs because it visualises almost all types of neural tube defects - it is affordable, non- invasive and is effective in 68-94% [1].

It is recommended to refer patients to genetic counselling and psychological treatment. Parents should be informed about their child’s disorders, prognosis, prenatal therapy, risk of the same disorder for second child. The mother's decision about the termination of pregnancy or full-term delivery should be consulted with specialists included obstetrician, clinical geneticist, paediatrician and psychologist [6]. When the foetus with neural tube defect will be continued to be delivered, the best method of delivery of the child must be considered.

MATERIAL AND METHODS

In our study, we analysed courses of pregnancies and methods of delivery of children with NTDs and we compared them with data from available literature. Study was conducted on patients from the II Department of Obstetrics and Gynaecology, Medical University in Warsaw, Poland.

RESULTS

Table 1 presents the case studies from our Department. All analysed cases ended up with vaginal delivery. The majority of patients did not experience complications during and after labour. They had also no recommendations for C-section.

Table 2 shows the data on delivery methods from different case studies found in literature. The majority of foetuses with neural tube defects were delivered vaginally.

DISCUSSION

Since most of the pregnancies with NTD worldwide are aborted, there is no data on the right method of delivery of children with NTDs.

There are well-known advantages of vaginal birth, such as: quicker recovery, shorter hospital stay and lower infection rate [7]. A caesarean section is associated with risks of postoperative adhesions, incisional hernias and wound infections. Other risks include severe blood loss, which may require a blood transfusion [26]. Moreover, the fact that vaginal birth does not leave an operation scar is very important for the patient's psychological wellbeing [6].

Machado et al. show a small number of cases when the pregnancies with NTDs were ended with a C-section. In these cases, there were indications for C-section, such as triplet pregnancy, failed labour induction of delivery and history of a previous C-section [8]. Tica et al. describe a case of a patient who was qualified to C-section because of breech position and uterine rupture [9]. There are no documented complications of vaginal birth of fetuses with NTDs in literature.

The recommendations of SOGC are that in cases of NTDs the delivery method should be chosen individually. The only exception to this rule is spina bifida, in which the C-section method should be preferred [1]. It should be underlined, that a history of previous C-sections is not a contraindication for vaginal delivery [7].

CONCLUSIONS

After careful analysis of this case reports and taking into consideration available literature, it could be said, that there are no significant contraindications to vaginal birth for the pregnancies complicated by acrania, anencaphaly or holoprosencephaly. For nearly all previously mentioned disorders C-section pretend to be less preferable way of delivery. Vaginal delivery is the better solution for children with defects, who do not have a chance of survival or fetuses that have died in utero. It is save and beneficial for the mother and has less negative consequences for the women and her future reproduction health.

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ABBREVIATIONS

AFAChE – amniotic fluid acetylcholinesterase
AFAFP – amniotic fluid alpha-fetoprotein
BPD – biparietal diameter
hCG – human chorionic gonadotropin
HPE – holoprosencephaly
NTDs – neural tube defects (NTDs)
MSAFP – maternal serum alpha-fetoprotein
SOGC – Society of Obstetricians and Gynaecologists

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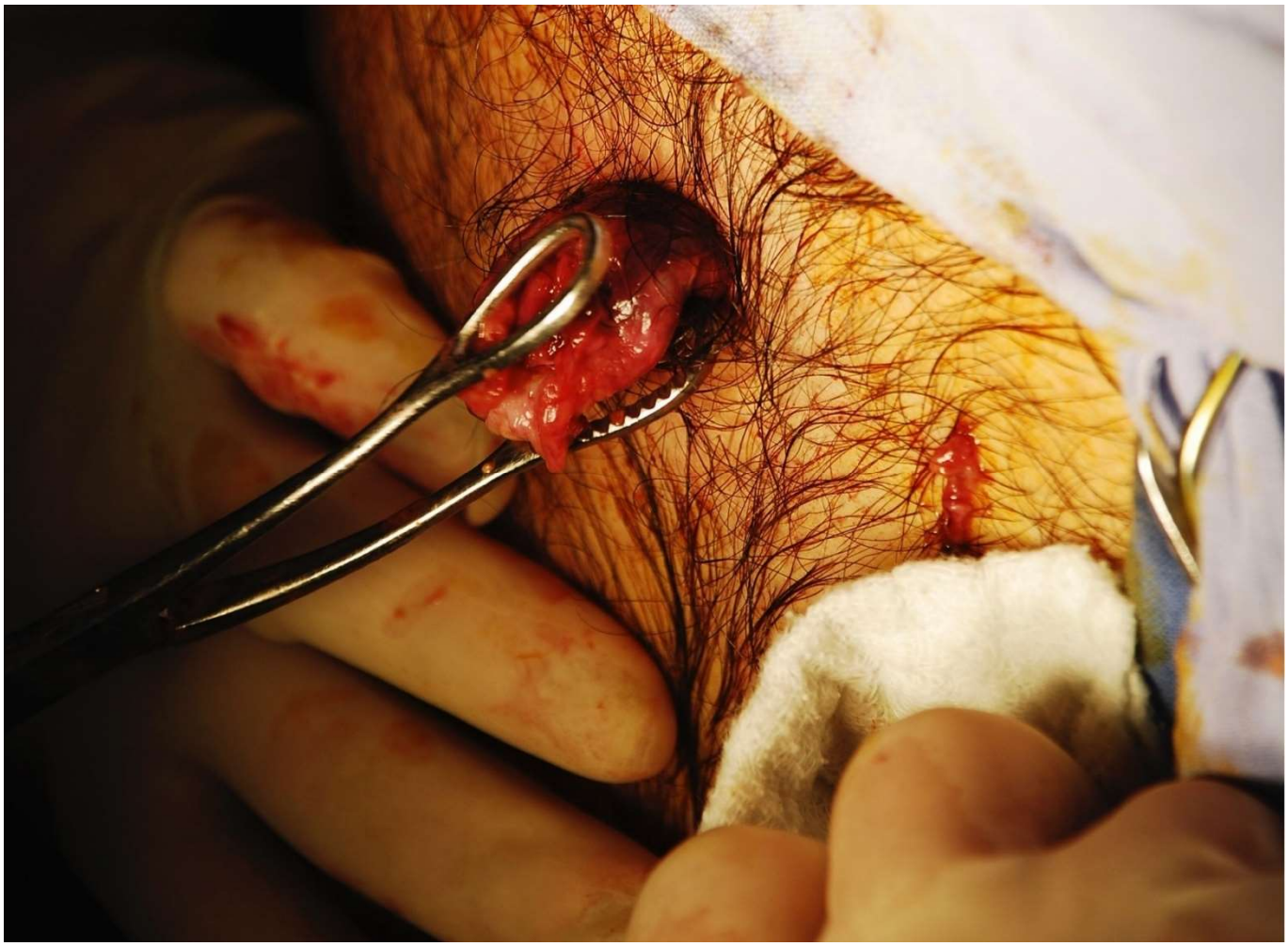
LIST OF TABLES

TAB. 1. CASE STUDIES FROM THE II DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, MEDICAL UNIVERSITY IN WARSAW, POLAND.

	CASE 1	CASE 2	CASE 3	CASE 4
Patient's history	G4 P3	G3 P2	G4 P4	G2 P2
Mother's age	32	26	33	29
Week of delivery	38 Hbd	41 Hbd	33 Hbd	41+3 Hbd
Birth weight	1420g	3290g	1600g	2880g
Complication during delivery	-	first-degree of perineal tear	-	cervical rupture, rupture of vagina, and urinary bladder rupture
Usage of drugs, treatment of infertility, chronic diseases	-	-	-	-
Acid folic suplementation	+	-	-	-
Diagnosed defects	acrania, brain herniation, circulatory insufficiency, preterm birth, one-sided cleft lip and palate, undergrowth of fingers of right hand	cleft lip and palate, lack off right eyball, lung's and kidney's hipoplasia, cardiomegaly	acrania, cleft spine and polyhydroamnios	holoprosencephaly, complete cleft lip and complete cleft palate
Survival time	47 h 20 min	1 h 50 min	intranatal death	intranatal death
	CASE 5	**CASE 6**	**CASE 7**	**CASE 8**
Patient's history	G1 P1	G4 P2	G2 P2	G2 P2
Mother's age	28	35	29	32
Week of delivery	42 Hbd	36 Hbd	36+6 Hbd	36+1 Hbd
Birth weight	3130g	1970g	2000g	1720g
Complication during delivery	-	episiotomy	episiotomy	-
Usage of drugs, treatment of infertility, chronic diseases	-	Lutein, Jodid and enoxaparin	-	-
Acid folic suplementation	+	-	-	-
Diagnosed defects	acrania	Patau'a Syndrome and Flatau'a Syndrome	Trisomy of 13 and heart defect (HLHS)	Patau'a Syndrome and polyhydroamnios
Survival time	intranatal death	65h	4h 30 min	intranatal death

TAB. 2. METHOD OF DELIVERY FROM DIFFERENT CASE STUDY FOUND IN LITERATURE.

NR	METHOD OF DELIVERY		DIAGNOSED DEFECTS	MEDICAL LITERATURE
	C- SECTION	VAGINAL BIRTH		
1	50	102	Central Nervous System Abnormalities (152 cases)	Foetal central nervous system anomalies: Frequency and foeto-maternal outcome, N. Amer, M., Amer, M. Kolkailah, M. Al-Dumairy, J Pak Med Assoc, Vol. 64 No. 11, November 2014: 1282-1286
2	15	52	Anencephaly (67 cases)	Neural tube defects in the Republic of Ireland in 2009-11, R. McDonnell, V. Delany, M.T. O'Mahony, C. Mullaney, B. Lee, M.J. Turner, Journal of Public Health Vol. 37, No. 1: 57-63
	38	46	Encephalocele (84 cases)	
3	13	117	Anencephaly (130 cases)	Anencephaly: Do the Pregnancy and Maternal Characteristics Impact the Pregnancy Outcome?, I.N. Machado, S.D. Martinez, R. Barini, ISRN Obstetrics and Gynecology Vol. 2012, Article ID 127490
4	1	0	Anencephaly	Case report: Anencephaly: pitfalls in pregnancy outcome and relevance of the prenatal exam, V.I. Tica, M. Beghim, I. Tica, M. Zaher, E. Beghim, Romanian Journal of Morphology and Embryology 2009, 50(2): 295-297
5	0	3	Holoprosencephaly	Prenatal findings of holoprosencephaly, Y. Hayashi, N. Suzumori, T. Sugiura, m. Sugiura-Ogasawara, Congenital Anomalies 2015; 55: 161-163



THE LOWER URINARY TRACT DYSFUNCTION AS A CHALLENGE IN RENAL TRANSPLANTATION

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ABSTRACT

After the implementation of complex urological reconstructive procedures, kidney transplantation in patients with no functioning urinary bladder has become possible. However, patients with anatomical and/or functional dysfunction of the lower urinary tract (LUT) are a challenge for the renal transplant surgeons. In patients with LUT, the native bladder may be suitable for transplantation, otherwise intestinal reconstruction or diversion may be required. Type of urinary diversion is priorly determined by patient's general condition, disease-specific health state, and his/her expectations for a better quality of life. Kidney transplant drainage into an ileal conduit for urinary diversion is an effective treatment for patients with end stage renal disease due to abnormal lower urinary tracts. The long-term graft and patient survival is comparable to that in the general transplant population.

BACKGROUND

The most common causes of end-stage renal disease (ESRD) in children are congenital anomalies of the kidney and urinary tract (CAKUT) [1]. The most common causes of CAKUT are:

- posterior urethral valves,
- vesicoureteral reflux,
- neurogenic bladder,
- bladder extrophy complex,
- prune belly syndrome [2].

In adult patients undergoing renal replacement therapy (RRT), CAKUT is much less common cause of ESRD accounting for less than 5% of a disease cases, dominated by diabetic and nondiabetic glomerulopathies [3].

In Poland, urological consultation of each candidate before entering the National Waiting List for the transplantation of the kidney or kidney with the pancreas is required. According to Churchill et al. [4], the following urological requirements should be met before patient qualification for kidney transplantation:

1. an adequate urine reservoir to store an adequate volume of urine (250 - 350 ml) at safe low pressure,
2. a proper urethral control mechanism ensuring proper urinary continence,
3. an unobstructed flow/outflow and an effective method of achieving complete emptying of the bladder using micturition or intermittent catheterisation.

In the past, patients with pathology of lower urinary tract (LUT) were disqualified from the kidney transplantation procedure. After the implementation of complex urological reconstructive procedures, kidney transplantation in patients with no functioning urinary bladder has become possible.

Nowadays, patients with anatomical and/or functional dysfunction of the lower urinary tract are a challenge for the renal transplant surgeons.

TIMING OF SURGICAL TECHNIQUE

In patients without pre-existing diversion or augmentation, an excellent timing of LUT reconstruction is datable. Patients requiring bladder augmentation or complete urinary diversion may have this procedure prior to, during or after renal transplantation. The enthusiasts of pre-transplant bladder augmentation or urinary diversion argue that this approach will ensure proper healing of the urinary tract in the absence of immunosuppressive regiments [5], [6], [7], [8]. Most investigators recommend performing the separate procedure at least 6 weeks prior to transplantation [9], [10], [11].

The proponents of post-transplant reconstruction of LUT consider that the optimal timing for reconstruction is that when renal function is stable and immunosuppression regiments are reduced [6].

KIDNEY POSITION

In patients with cystoplasty, the transplant kidney orientation is similar to standard transplants [2]. In patients with urinary diversion, placing the kidney in an upside-down position is usually preferred to reduce the distance of the transplanted ureter and provide a smooth-running course with no ureteral kinking [12].

URINARY DIVERSION (UD)

In patients with lower urinary tract dysfunction, the native bladder may be suitable for transplantation, otherwise intestinal reconstruction or diversion may be required [13], [14], [15]. Type of UD is priorly determined by patient's general condition, disease-specific health state, and his/her expectations for a better quality of life [16].

Cystoplasty is usually a last resort option for patients with neurogenic bladder if more conservative treatment options have failed. Various segments of the gastrointestinal tract (stomach, ileum, colon) have been used to augment the native bladder [2]. The incidence of chronic bacteriuria and urinary tract infections is high in patients undergoing cystoplasty, but many patients accept this to avoid a stoma [17].

There are two main categories of urinary diversion methods [18]:

1. continent reservoir
   - continent orthotopic bladder substitution (neobladder),
   - heterotopic continent bladder replacement (pouch),
   - ureterosigmoidostomy;
2. incontinent reservoir
   - intestinal conduits,
   - ureterocutaneostomy.

Neobladder

Continent orthotopic bladder substitution (neobladder) is the treatment of choice in patients with an indication for cystectomy with curative intent. The reservoir, consisted of 50 to 70 cm of ileum, is placed in the pelvis minor and voided by increasing intra-abdominal pressure. Urine continence is obtained through the patient's own sphincter [18].

Pouch

Heterotopic continent bladder replacement (pouch) is usually created from an ileal or ileocecal segment, which is emptied by self-catheterization through a permanent stoma. This form of urinary diversion is used if the reservoir cannot be connected to the urethra [18]. The continence mechanism usually relies on a submucosally embedded appendix, an ileum invagination nipple or Yang-Monti channel [19].

There are many urological complex procedures for heterotopic continent bladder replacement:

- the cutaneous appendicovesicostomy, initially described by Mitrofanoff in 1980 [20],
- the Yang-Monti procedure [21], which uses small pieces of ileum to create cutaneous ileovesicostomy,

- the Indiana pouch, comprised of approximately 30 cm of the proximal right colon for pouch formation in continuity with 10 cm of the terminal ileum for the catheterizable channel and utilizing the ileal cecal valve for continence [22],
- the Florida pouch, which uses a detubularized right colonic segment as a reservoir, a tapered external limb reinforced at the ileocecal valve level allowing for continent catheterization [23].

Ureterosigmoidostomy

The idea of diverting the urine into the rectum is usually attributed to Simon [24]. Ureterosigmoidostomy is a surgical procedure whereby the ureters are implanted into the rectosigmoid colon. The anal sphincter preserves continence [18]. For the first half of the 20th century, ureterosigmoidostomy was the prime method of urinary diversion [25], before the era of continent cutaneous diversion and neobladders, specifically in children.

Three general groups of ureterocolic anastomosis methods are widely used [26]:

Tubular implantation with submucosal tunnel (Cof-

fey's procedure,

- tubular implantation with submucosal tunnel (Cofey's procedure),
- ureterocolic implantation by direct end-to-side anastomosis: spatulated ureter ends are anastomosed in a single layer to incision edges in the colon (Nesbit procedure) or the ureter ends are anastomosed circularly in 2 layers with interrupted sutures (Cordonnier procedure),
- direct end-to-side implantation with tunnel (Petit-Laedbetter procedure).

A known complication of urinary diversion with gastrointestinal substitution is adenocarcinoma. The dominant theory of pathogenesis is understood as the formation of the carcinogen nitrosamine due to exposure of urine [27]. A median interval between ureterosigmoidostomy and diagnosis of an adenocarcinoma of the sigmoid colon has been reported to be at 26 years, with an average patient age of 33 years [28]. Kalble et al. compared the tumor risk of patients with ureterosigmoidostomy in a single institution with the cancer statistics of two German counties and found the risk to be 500-fold in the group aged 25–30 yr and 8-fold at 55–60 yr [29].

In some groups of patients, particularly young adults with prognosis of longer life expectancy, ureterosigmoidostomy should be conducted as a last resort. Patients with ureterosigmoidostomy should be carefully followed up, especially in terms of colorectal cancer development [2].

Intestinal conduits

The ileal conduit is the most commonly used type of incontinent UD [30], [31]. An ileal segment of about 15 cm length is separated and laterally brought out as a stoma in the lower abdomen. End-to-side single-layer anastomosis of the kidney transplant ureter to the intestinal loop is preferred [9]. Creating an ileal conduit is technically more straightforward and the procedure takes less time than a continent bladder substitution system [18].

Although about 40 methods of urinary diversion are known, an ileal conduit has become the most used form of urinary diversion in kidney transplantation [32]. An ileal conduit urinary diversion has sometimes been referred to as the Bricker ileal conduit after its inventor, Eugene M. Bricker. In 1947, Bricker performed an supravesical urinary diversion involving the implantation of ureters into the isolated ileum loop, the distal end of which was implanted in the skin [33].

Ureterocutaneostomy

Ureterocutaneostomy is a type of incontinent cutaneous urinary diversion. This type of UD is usually preferred as a temporary diversion in infants/children, whose metabolic status is inadequate for reconstructive surgery or in palliative care of bladder carcinoma patients. Successful renal transplantation in patients with long-standing cutaneous ureterostomies have been reported [34], [35], [36].

DISCUSSION

In the past, patients with pathology of lower urinary tract were disqualified from the kidney transplantation procedure. Initially introduced by a French pediatric surgeon, Paul Mitrofanoff, in 1980 the continent catheterizable conduit (CCC) using appendicovesicostomy, revolutionized the treatment of patients who need lower urinary tract reconstruction [20], [37]. Since that time, the technique has been modified to incorporate myriad donor tissues, catheterization sites, continence valves and skin site modifications [38]. Continent urinary diversion (CUD) and enterocystoplasty (ECP) improve quality of life and body image of the patients, in whom all attempts at conservative management have failed to achieve continence [39].

The first successful kidney transplantation into an ileal conduit was reported by Kelly et al. in 1996 [40]. Rates of renal transplantation into patients with supravesical diversion range from 0.4% to 2.3% [9], [41]. Percentage of renal transplantation into a prior bladder augmentation rates of about 1% [42].

Mitrofanoff appendicovesicostomy provides good results in children. It ensures good continence, a low complication rate and satisfactory school and social readaptation [43]. In adults, Mitrofanoff urinary diversion is effective in offering continence. However, this it needs to be balanced against the need for subsequent additional interventions for stone formation, stomal stenosis and urinary tract infections on an individual basis [44].

Rigamonti et al. [10] confirm that bladder reconstruction before transplantation enables even the most severely compromised patients to receive a renal allograft successfully. 87.5% of grafts were functioning at the end of follow-up period of 15 years. Graft survival rates were 94.1%, 80.7%, 80.7% and 80.7% at 1, 5, 10 and 15 years, respectively.

Surange et al. [41] reported their own experience with renal transplantation into ileal conduits. Researchers analysed a cohort of 54 patients with kidney

transplantation into an ileal conduit between January 1980 and August 2002. Median patient age was 28 years (range from 1 to 63 years). Pediatric recipients accounted for 24.1%. There were 12 living related- and 47 deceased-donor kidneys transplanted. Patient and graft survival following transplantation into an ileal conduit were compared with that in the 2,579 other transplants done at this center. Graft survival rates were 90%, 63% and 52% at 1, 5 and 15 years of follow up, respectively. Recipients' survival rates were 95%, 83% and 69% at 1, 5 and 15 years follow up, respectively. Symptomatic urinary tract infection was noted in 65% of the patients.

McLoughlin et al. retrospectively reviewed the allograft and surgical outcome of renal transplantation in the recipients with an ileal conduit. 17 patients with an ileal conduit, who received a deceased-donor renal transplant between January 1986 and December 2012, were reported. Sixteen of 17 grafts functioned immediately; one patient had primary non-function secondary to vascular thrombosis. 76.5% grafts were functioning at a mean follow-up period of 105 months. 30% of patients had seven episodes of urosepsis requiring hospital admission.

Hatch et al. [46] reviewed the experience of sixteen transplant centres, which transplanted 31 kidneys for 30 children. Graft survival rates were 90%, 78% and 60% at 1, 5 and 10 years, respectively.

According to a case-control study from the four transplantation centres in Sweden, patients with ileal conduits or continent reservoirs have similar graft and patient survival rates as the general kidney transplant population [5].

Aikawa et al. [47] concluded that lower urinary tract abnormality is not always a risk factor for pediatric renal transplantation. However, a preoperative evaluation is important to choose the best option for urinary diversion.

Srinivisan et al. [48] revealed the long-term outcomes of kidney transplant recipients with bladder dysfunction. Researchers compared outcomes of 80 patients with bladder dysfunction, 21 patients with bladder substitute or urinary diversion and 1652 patients with normal bladder function. Patient survival at 1 and 5 years was 96.2% and 84.3% for normal bladder function; 91.2% and 75.2% for bladder surgery; and 96.2% and 90% for bladder dysfunction, respectively. There were no significant differences between bladder groups. However, kidney transplant recipients with prior bladder surgery have an increased risk of graft failure.

CONCLUSIONS

Kidney transplant drainage into an ileal conduit for urinary diversion is an effective treatment for patients with end stage renal disease due to abnormal lower urinary tracts. The long-term graft and patient survival is comparable to that in the general transplant population.

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ABBREVIATIONS

CAKUT – congenital anomalies of the kidney and urinary tract
CCC – continent catherizable conduit
CUD – continent urinary diversion
ECP – enterocystoplasty
ESRD – end-stage renal disease
LUT – lower urinary tract
UD – urinary diversion

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