Thieme

Differences between Current Clinical Practice and Evidence-Based Guideline Recommendations Regarding Tocolysis – an Austria-wide Survey

Unterschiede zwischen der aktuellen klinischen Praxis und evidenzbasierten Leitlinienempfehlungen zur Tokolyse: eine österreichweite Erhebung

OPEN ACCESS

Authors

Sabine Enengl[1,2], Werner Rath[3], Sven Kehl[2,4], Peter Oppelt[1], Andreas Mayr[5], Annika Stroemer[5], Teresa Eichinger[1], Julia Lastinger[1], Patrick Stelzl[1]

Affiliations

1 Department of Gynecology, Obstetrics, and Gynecological Endocrinology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria
2 Friedrich-Alexander-University Erlangen-Nürnberg, FAU, Erlangen, Germany
3 Medical Faculty of Gynecology and Obstetrics, University Clinic Schleswig-Holstein, Kiel, Germany
4 Department of Obstetrics and Perinatal Medicine, Hallerwiese Hospital, Nürnberg, Germany
5 Institute for Medical Biometry, Informatics and Epidemiology, Medical Faculty, University of Bonn, Bonn, Germany

Keywords

preterm birth, tocolysis, survey, clinical practice, guideline recommendations

Schlüsselwörter

Frühgeburt, Tokolyse, Erhebung, klinische Praxis, Leitlinienempfehlungen

received 16.9.2024
accepted after revision 19.10.2024
published online 28.11.2024

Bibliography

Geburtsh Frauenheilk 2025; 85: 47–55
DOI 10.1055/a-2446-1828
ISSN 0016-5751

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Correspondence

Sabine Enengl, MD
Department of Gynecology, Obstetrics, and Gynecological Endocrinology
Kepler University Hospital, Johannes Kepler University Linz
Altenberger Straße 69
4040 Linz, Austria
sabine.enengl@gmx.at

ABSTRACT

Introduction

To evaluate the adherence of Austrian obstetricians to national guideline recommendations by investigating data on the current practice of tocolysis regarding indications, timing and monitoring of tocolysis, choice of tocolytics and serious side effects, maintenance tocolysis, support of decision-making and recommendations at patient's discharge from the hospital.

Materials and Methods

78 obstetric departments in Austria were invited to participate in a nationwide survey between June 5th and August 31st 2023 by answering a web-based questionnaire about clinical standards. The survey was conducted approximately one year after implementation of the AWMF Guideline "Prevention and Therapy of Preterm Birth" 015-025. Collected data were analyzed descriptively by performing measures of frequency. Fisher's exact test was used for group comparison.

Results

The response rate was 69.2% (33.3% perinatal centers, 66.7% standard care). The most important indication of tocolysis were ≥ 4 contractions within 20 minutes of CTG tracing, as stated by 26 (48.1%) of the respondents; the AWMF Guideline 015-025 (2022) was the most important

decision-making support for tocolytic treatment (61.1%). 19 (35.2%) of obstetric units started tocolysis earliest at 23 + 0 weeks of gestation. Atosiban was the first-line tocolytic drug used by 43 (79.6%) of obstetric units, followed by nifedipine (n = 7, 13.0%); 49 of 54 obstetric units (90.7%) stated to perform maintenance tocolysis, among these 46 (93.9%) not routinely but on special indications (e.g. placenta previa). Serious side effects were observed by 77.8% of the respondents, mostly associated with the use of hexoprenaline.

Conclusions
Our survey revealed considerable discrepancies between evidence-based guideline recommendations and daily clinical practice in Austrian hospitals.

ZUSAMMENFASSUNG

Einleitung
Ziel dieser Studie war es, die Einhaltung von Empfehlungen in nationalen Leitlinien durch Geburtshelfer*innen in Österreich zu bewerten. Dazu wurden Daten zur aktuellen Praxis der Tokolyse hinsichtlich Indikation, Zeitpunkt und Überwachung der Tokolyse, Wahl des Tokolytikums und schwerwiegende Nebenwirkungen, Erhaltungstokolyse, Entscheidungshilfe und Empfehlungen bei Entlassung der Patientin aus dem Krankenhaus untersucht.

Material und Methoden
Zwischen dem 5. Juni und dem 31. August 2023 wurden 78 geburtshilfliche Abteilungen in Österreich zur Teilnahme an einer landesweiten Erhebung aufgefordert, indem sie einen Online-Fragebogen über klinische Standards beantworten sollten. Die Erhebung wurde ungefähr 1 Jahr nach Einführung der AWMF-Leitlinie „Prävention und Therapie der Frühgeburt“ 015-025 durchgeführt. Die deskriptive Analyse der erhobenen Daten erfolgte mittels Häufigkeitsanalysen. Der Exakte Fisher-Test wurde für Gruppenvergleiche eingesetzt.

Ergebnisse
Die Rücklaufquote betrug 69,2% (33,3% Perinatalzentren, 66,7% Zentren der Grund- und Regelversorgung). Laut 26 (48,1%) der Befragten war die wichtigste Indikation zur Einleitung einer Tokolyse eine CTG-Aufzeichnung von ≥ 4 Wehen/20 Minuten; die AWMF-Leitlinie 015-025 (2022) stellte die wichtigste Entscheidungshilfe für eine tokolytische Behandlung dar (61,1%). 19 (35,2%) der geburtshilflichen Abteilungen haben frühestens in der 23 + 0 Schwangerschaftswoche mit einer Tokolyse begonnen. Tokolytikum der ersten Wahl war das Mittel Atosiban, das von 43 (79,6%) geburtshilflichen Abteilungen eingesetzt wurde, gefolgt von Nifedipin (n = 7, 13,0%); 49 von 54 geburtshilflichen Abteilungen (90,7%) gaben an, dass sie eine Erhaltungstokolyse verabreichen, wobei 46 (93,9%) diese nicht routinemäßig, sondern nur bei besonderen Indikationen (z. B. Placenta praevia) einsetzen. Schwerwiegende Nebenwirkungen wurden von 77,8% der Umfrageteilnehmer*innen beobachtet, meist in Verbindung mit dem Einsatz von Hexoprenalin.

Schlussfolgerungen
Unsere Erhebung zeigte beträchtliche Diskrepanzen zwischen den evidenzbasierten Empfehlungen der Leitlinie und der täglichen klinischen Praxis in österreichischen Krankenhäusern auf.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACS	antenatal corticosteroids
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
COX	Cyclooxygenase
fFN	fetal fibronectin
IGFBP-1	insulin-like growth factor-binding protein-1
NICE	National Institute for Health and Care Excellence
NO	nitric oxide
OC	obstetric clinic
PAMG-1	placental alpha microglobulin-1
PNC	perinatal care center
PPROM	preterm premature rupture of membranes
PTB	preterm birth
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomized controlled trial
SOP	standard operating procedure

Introduction

Preterm birth (PTB) accounting for five to 12% of deliveries in Europe is one of the major causes of neonatal morbidity and mortality [1]. Its etiology is multifactorial [2]. In 2022, the rate of preterm birth in Austria was 7.2%, 1.9% of live births were PTBs before 34 weeks of gestation [3]. Spontaneous onset of labor, preterm premature rupture of membranes (PPROM) or medically indicated PTBs due to maternal or fetal conditions are the main contributors [4]. Gestational age is strongly associated with neonatal mortality and morbidity, in particular, with higher rates of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) or neurologic morbidities occurring especially in extreme PTBs [5].

Tocolysis is a mainstay in the prevention of PTB and recommended by all international guidelines to prolong pregnancy by at least 48 hours to complete a full course of antenatal corticosteroids (ACS) and to ensure in utero transfer of the pregnant woman to a perinatal center (PNC) before 34 weeks of gestation [6].

According to meta-analyses prolongation of pregnancy can be achieved with the use of tocolytics by 48 hours in approximately 80 % of cases [7, 8, 9]. Tocolysis after PPROM remains a matter of debate [10]. Maintenance tocolysis, mostly defined as continuation of tocolytic treatment beyond 48 hours, is not recommended by international guidelines due to the lack of evidence that it improves neonatal outcomes [7, 8, 9].

This can be explained by a considerable heterogeneity among studies including study design, inclusion and exclusion criteria, use of different tocolytics and doses as well as different outcome parameters [6]. However, maintenance tocolysis is commonly used in clinical practice for numerous reasons, hence maintenance tocolysis still remains a controversial issue.

Despite the availability of international and national guidelines, our and other groups have covered low adherence of obstetricians in different countries to evidence-based recommendations [11, 12, 13, 14, 15]. The aim of our cross-sectional study was to evaluate current clinical practice in Austrian obstetric units of higher and lower perinatal care levels and to compare the results with actual guideline recommendations.

Materials and Methods

All 78 obstetric departments in Austria were invited to participate in a nationwide survey. Since 2017, the obstetric units are categorized to four perinatal care levels according to specified standards of the Austrian Structural Plan for Health (Österreichischer Strukturplan Gesundheit OESG): PNC level I or II, obstetric clinic (OC) level I with ≥ 500 and OC level II with < 500 deliveries annually. The head of each unit received a link to a web-based questionnaire via email containing information on the purpose of the study. The questionnaire was developed according to international guidelines. The questionnaire was created based on the German survey conducted by our study group [16] and was pre-tested by three experts and modified to warrant comprehensibility and feasibility. Each participant was only allowed to complete the questionnaire once during an 88-days study period (June 5th – August 31st 2023). Reminders with an interval of four weeks were sent twice. The questionnaire consisted of 20 multiple choice and open-ended questions addressing the following items: baseline characteristics (3 questions), indications for tocolysis (2 questions), timing of tocolysis and ACS (3 questions), choice of tocolytics (3 questions), serious side effects (1 question), maintenance tocolysis (4 questions), tocolysis in PPROM (1 question), monitoring of tocolysis (1 question), guidance for decision-making (1 question) and recommendations at patient's discharge from the hospital (1 question).

The study was conducted anonymously without financial compensation. Only one participant per department was accepted. No personal data were collected. Only complete questionnaires were included into final statistical analysis.

Statistical analysis

Data was descriptively analyzed by performing measures of frequency. Fisher's exact test was used for group comparison. $P < 0.05$ was considered statistically significant.

▶**Table 1** Characteristics of responding clinics.

	n	%
Level of obstetric clinic (n = 54)		
Perinatal center (PNC) Level I	9	16.7
Perinatal center (PNC) Level II	9	16.7
Obstetric clinic (OC) I (≥ 500 deliveries/year)	26	48.1
Obstetric clinic (OC) II (< 500 deliveries/year)	10	18.5
Annual delivery rate		
< 1000	29	53.7
1000–2000	17	31.5
2001–3000	4	7.4
> 3000	4	7.4
Clinical position of interviewed person		
Head of clinic	35	64.8
Leading senior physician	9	16.7
Senior physician	5	9.3
Attending physician	4	7.4
Resident physician	1	1.9

Results

Baseline characteristics of responding obstetric units

78 Austrian obstetric departments were invited to take part in the survey, 54 clinics completed the questionnaire, accounting for a response rate of 69.2 %. Ten clinics started the survey without completion. One third of responding clinics were PNC level I or II (33.3 %), two thirds were OC level I or II (66.7 %). The characteristics of responding clinics and interviewed personnel are shown in ▶ **Table 1**.

Indications for tocolysis

Indications for tocolysis were ≥ 4 contractions within 20 minutes (n = 26, 48.1 %), shortening of cervical length ≤ 25 millimeters (n = 14, 25.9 %), a positive biomarker test (n = 9, 16.7 %) or subjective contractions (n = 5, 9.3 %) (▶ **Table 2**).

Decision-making support

The AWMF Guideline "Prevention and Therapy of Preterm Birth" 015-025 was the most important decision-making support regarding tocolytic treatment (n = 33, 61.1 %), followed by hospital specific standard operating procedures (SOPs)/algorithms (n = 15, 27.8 %). Further details are shown in ▶ **Table 3**.

Timing of tocolysis and ACS

Most of obstetric units (n = 19, 35.2 % – PNC: 38.9 %, OC: 33.3 %) started tocolysis earliest at gestational week 23 + 0, 29.6 % (n = 16 – PNC: 38.9 %, OC: 25.0 %) at 22 + 0 gestational weeks, 22.2 % (n = 12 – PNC: 16.7 %, OC: 25.0 %) at 23 + 5 gestational weeks and

▶**Table 2** Which is your most important clinical parameter for indicating tocolysis (single choice)?

	PNC Level I–II (n = 18)		OC I–II (n = 36)		Total (n = 54)		p-value
	n	%	n	%	n	%	
Cervical length ≤ 25 mm	5	27.8	9	25.0	14	25.9	1.00
≥ 4 contractions within 20 min	6	33.3	20	55.6	26	48.1	0.16
Preterm birth/late miscarriage in patient's history	0	0.0	0	0.0	0	0.0	1.00
Positive biomarker testing (PAMG-1, fFN, IGFBP-1)	5	27.8	4	11.1	9	16.7	0.14
Subjective contractions	2	11.1	3	8.3	5	9.3	1.00

fFN = fetal fibronectin; IGFBP-1 = insulin-like growth factor-binding protein-1; OC = obstetric clinic; PAMG-1 = placental alpha microglobulin-1; PNC = perinatal care center

▶**Table 3** On which guidance do you base your decision for tocolysis (single choice)?

	PNC Level I–II (n = 18)		OC I–II (n = 36)		Total (n = 54)		p-value
	n	%	n	%	n	%	
Clinical intern SOP/algorithm	6	33.3	9	25.0	15	27.8	0.54
National guidelines (AWMF 015-025)	10	55.6	23	63.9	33	61.1	0.57
Personal experience	1	5.6	2	5.6	3	5.6	1.00
Professional experience of supervising/more experienced colleagues	0	0.0	1	2.8	1	1.9	1.00
International guidelines (e.g. ACOG, RCOG, NICE)	1	5.6	1	2.8	2	3.7	1.00

ACOG = American College of Obstetricians and Gynecologists; AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; NICE = National Institute for Health and Care Excellence; OC = obstetric clinic; PNC = perinatal care center; RCOG = Royal College of Obstetricians and Gynaecologists; SOP = standard operating procedure

13.0 % (n = 7 – PNC: 5.6 %, OC: 16.7 %) at 24 + 0 gestational weeks. There were no significant differences between PNCs und OCs.

66.7 % of obstetric units (n = 36 – PNC: 77.8 %, OC: 61.1 %) stopped tocolysis at 34 + 0 gestational weeks, 11.1 % (n = 6 – PNC: 5.6 %, OC: 13.9 %) at 35 + 0 gestational weeks, 16.7 % (n = 9 – PNC: 11.1 %, OC: 19.4 %) at 36 + 0 gestational weeks and even 5.6 % (n = 3 – PNC: 5.6 %, OC: 5.6 %) at 37 + 0 weeks of gestation. There were no significant differences between PNCs und OCs.

38.9 % (n = 21 – PNC: 50.0 %, OC: 33.3 %) performed administration of ACS concomitantly with tocolysis beginning at 23 + 0 weeks of gestation, 16.7 % (n = 9 – PNC: 11.1 %, OC: 19.4 %) at 23 + 5 gestational weeks, 14.8 % (n = 8 – PNC: 16.7 %, OC: 13.8 %) at 22 + 0 gestational weeks, 13.0 % (n = 7 – PNC: 0 %, OC: 19.4 %) at 24 + 0 weeks and 16.7 % (n = 9 – PNC: 22.2 %, OC: 13.8 %) of obstetric units stated to confer with a nearby PNC before initiating ACS. There was again no significant difference between PNCs and OCs.

Choice of tocolytics

The first line tocolytic was stated to be atosiban in 79.6 % (n = 43) of the respondents, followed by oral nifedipine in 13.0 % (n = 7), and intravenous hexoprenaline as bolus in 5.6 % (n = 3) or as continuous administration in 1.9 % (n = 1). Most common criteria for the choice of a specific tocolytic agent were efficiency (n = 47, 87.0 %), low maternal side effects (n = 45, 83.3 %), recommendations from guidelines (n = 41, 75.9 %) and approval (n = 34, 63.0 %). There were no statistically significant differences between PNCs and OCs, as shown in ▶ **Table 4**.

Maintenance tocolysis

49 of 54 obstetric units (90.7 %) stated to perform maintenance tocolysis (16 PNCs, 33 OCs), among these 93.9 % (n = 46) on special indications such as placenta previa, fetal congenital anomalies to prolong pregnancy for further interventions or amniotic sac prolapse; 46.9 % (n = 23) conducted maintenance tocolysis in threatened preterm birth < 29 + 0 weeks of gestation. There were no significant differences between PNCs and OCs regarding the

▶**Table 4** What is the first line tocolytic at your clinic (single choice)? Please state your most important criteria for the choice of the tocolytic drug (multiple choice)!

	PNC Level I–II (n = 18)		OC I–II (n = 36)		Total (n = 54)		p-value
	n	%	n	%	n	%	
First line tocolytic							
Hexoprenaline continuously	0	0.0	1	2.8	1	1.9	1.00
Nifedipine	2	11.1	5	13.9	7	13.0	1.00
Atosiban	16	88.9	27	75.0	43	79.6	0.30
Hexoprenaline bolus	0	0.0	3	8.3	3	5.6	0.54
Indomethacin	0	0.0	0	0.0	0	0.0	1.00
Most important criteria							
Approval	14	77.8	20	55.6	34	63.0	0.14
Efficiency	17	94.4	30	83.3	47	87.0	0.40
Low maternal side effects	16	88.9	29	80.6	45	83.3	0.70
Low fetal side effects	9	50.0	19	52.8	28	51.9	1.00
Practicability	4	22.2	13	36.1	17	31.5	0.36
Drug costs	1	5.6	4	11.1	5	9.3	0.65
Guideline recommendation	13	72.2	28	77.8	41	75.9	0.74

OC = obstetric clinic; PNC = perinatal care center

▶**Table 5** Do you regularly perform maintenance tocolysis beyond 48 hours, and if yes for which reason(s) (multiple choice)?

	PNC Level I–II (n = 18)		OC I–II (n = 36)		Total (n = 54)		p-value
	n	%	n	%	n	%	
No	2	11.1	3	8.3	5	9.3	
Yes	**16**	**88.9**	**33**	**91.7**	**49**	**90.7**	**1.00**
On patient's request	2	12.5	1	3.0	3	6.1	0.25
On special indications (e.g. placenta previa, amniotic sac prolapse)	15	93.8	31	93.9	46	93.9	1.00
In early weeks of gestation (< 29 + 0)	8	50.0	15	45.5	23	46.9	1.00
Only in case-by-case decisions	5	31.3	5	15.2	10	20.4	0.26

OC = obstetric clinic; PNC = perinatal care center

use of maintenance tocolysis (▶ **Table 5**). 55.1 % (n = 27) of obstetric units conducting maintenance tocolysis reported to use atosiban, 22.4 % (n = 11) oral nifedipine, 16.3 % (n = 8) hexoprenaline and 6.1 % (n = 3) intravenous magnesium sulfate. Atosiban was significantly more often used in PNCs than in OCs (81.3 % vs. 42.4 %; p = 0.01) and betamimetics significantly more often in OCs than in PNCs (24.2 % vs. 0.0 %; p = 0.04). Bedrest during maintenance tocolysis was recommended by 68.5 % of obstetric units.

Tocolysis in PPROM

52 of 54 clinics performed tocolysis in cases of PPROM, among these 34 (65.4 % – PNC: 50 %, OC: 73.5 %) only for 48 hours to complete a full course of ACS, and 28.8 % (n = 15 – PNC: 38.9 %, OC: 23.5 %) conducted tocolysis in patients with PPROM in a case-by-case decision (e.g. in association with preterm labor and/or pregnancy < 29 + 0 weeks of gestation). Three clinics (5.8 % – PNC: 11.1 %, OC: 2.9 %) stated to generally perform tocolysis longer

▶**Table 6** What are your most important recommendations after tocolysis when patients are discharged from hospital (multiple choice)?

	PNC Level I–II (n = 18)		OC I–II (n = 36)		Total (n = 54)		p-value
	n	%	n	%	n	%	
Bedrest	2	11.1	3	8.3	5	9.3	1.00
Progesterone (oral or vaginal)	14	77.8	22	61.1	36	66.7	0.36
Close follow-ups at patient's health provider	12	66.7	28	77.8	40	74.1	0.51
Close follow-ups in your clinic	10	55.6	9	25.0	19	35.2	0.04
Sick leave/employment prohibition	13	72.2	22	61.1	35	64.8	0.55
Oral tocolysis (e.g. nifedipine)	2	11.1	4	11.1	6	11.1	1.00
Activity restriction	15	83.3	32	88.9	47	87.0	0.67

OC = obstetric clinic; PNC = perinatal care center

than 48 hours in patients with PPROM. Regarding this issue there were no statistically significant differences between levels of care.

Monitoring of tocolysis

Repeated transvaginal sonography of cervical length measurement was the most frequent method to monitor tocolytic efficacy (n = 47, 87.0 % – PNC: 88.9 %, OC: 86.1 %), followed by tocography (n = 46, 85.2 % – PNC: 77.8 %, OC: 88.9 %), and 37 (68.5 % – PNC: 72.2 %, OC: 66.7 %) of the respondents stated to ask the patients for subjective contractions.

Serious side effects of tocolytics

77.8 % of the respondents (PNC: 22.2 %, OC: 22.2 %) reported to have experienced serious side effects, mostly associated with the use of hexoprenaline (cardiac arrhythmia, severe hypokalemia, pulmonary edema). Severe hypotension and/or significant tachycardia were observed with the use of nifedipine by 5 (9.3 % – PNC: 5.6 %, OC: 11.1 %) of the respondents including one case of pulmonary edema. Minor side effects as headache and dizziness, particularly, if the initial bolus was administered rapidly, were stated to be associated with the use of atosiban (n = 17, 31.5 % – PNC: 27.8 %, OC: 33.3 %).

Recommendations at patient's discharge from the hospital

These recommendations are listed in ▶ **Table 6**. Activity restriction (n = 47, 87.0 %), close surveillance by the patient's health care provider (n = 40, 74.1 %) and daily administration of progesterone (n = 36, 66.7 %) were the most frequent recommendations at patient's discharge from the hospital.

Discussion

Tocolytic treatment is one of the most common procedures in obstetrics. Despite the widespread availability of evidence-based recommendations there are considerable discrepancies between these recommendations and clinical practice. This has been shown by numerous surveys from different countries [11, 13, 14, 15] and also by a recent German-wide survey [12, 16] which was conducted one year after implementation of the AWMF Guideline 015-025 "Prevention and Treatment of Preterm Birth" [7].

Indications for tocolysis vary among different international guidelines. While the AWMF Guideline 015-025 recommends spontaneous, regular contractions (≥ 4 within 20 minutes) in association with cervical shortening/dilatation as the leading criterion [7], only 48.1 % of the Austrian obstetric units were in accordance with this guideline recommendation, which was similar to the 42.5 % in the German survey [12]. In addition to that, cervical shortening without contractions should not be a reason for tocolysis, but is stated to be the main indication for 25.9 % of clinics. Also, repeated transvaginal ultrasound is not recommended to monitor the tocolytic efficacy, but is performed by 87 % of units. In this context it has to be considered that 61.1 % of respondents stated to use the AWMF Guideline 015-025 for decision-making, which was in line with the German survey. Interestingly, even 11.1 % of PNCs state that subjective contractions are their main indication for tocolysis. The beginning of tocolysis was in accordance to guideline recommendations; 33.3 % of the obstetric units continued tocolysis up to 37 weeks of gestation, contrasting to the national and other guideline recommendations. Calcium channel blockers as nifedipine are the preferred tocolytic agent in Germany (49.1 % of obstetric units) as well as in other countries [13, 15] and recommended as first-line tocolytic drug by numerous guidelines [17, 18, 19, 20], however, nifedipine was stated to be the first-line tocolytic drug by only 13.0 % of the Austrian obstetric units, while 79.6 % stated atosiban to be the tocolytic of choice.

Atosiban and nifedipine have shown to be equally effective in prolonging pregnancy by 48 hours and no significant differences between both were found regarding perinatal and neonatal outcomes as well as long-term infant morbidity [21, 22, 23, 24, 25]. The advantage of atosiban over nifedipine is the lower rate of maternal side effects [23], the disadvantages are the higher purchase price and the necessity of intravenous administration associated with immobilization thus lowering patient's acceptance compared

to orally given nifedipine [6]. In accordance with guideline recommendations none of the obstetric units stated to use orally applied magnesium for tocolysis [7, 17, 18, 19, 26]. Efficacy, low maternal side effects and guideline recommendation were the most important criteria for the choice of the tocolytic agent.

Since there is insufficient evidence from qualified RCTs that maintenance tocolysis reduces neonatal morbidity and mortality, current guidelines consistently do not recommend maintenance tocolysis [27, 28]. Surprisingly, 90.7 % of obstetric units stated to perform maintenance tocolysis, the majority of them only on special indications.

Independently, if maintenance tocolysis is taken into consideration, the question which tocolytic drug may be suitable is unsolved. Briefly, due to the loss of efficacy through tachyphylaxis and the high rate of maternal side effects betamimetics should be omitted for maintenance tocolysis [27]. According to a meta-analysis the use of oral nifedipine beyond 48 hours compared to placebo/no treatment has shown to be not associated with a significant prolongation of pregnancy and a significant reduction of neonatal morbidity [29]. Cyclooxygenase (COX) inhibitors such as indomethacin should only be given for 48 hours until 32 weeks of gestation and nitric oxide (NO) donators have never been investigated for maintenance tocolysis in randomized controlled trials (RCTs) [27]. Data on the use of atosiban for maintenance tocolysis are limited to only one RCT in 2000 [30]. Although the interval from start of therapy to the first recurrence of labor was prolonged, there was no difference in neonatal outcome and preterm birth rates in this study. Also, it has to be mentioned that Atosiban was given subcutaneously, whereas in Austria it is routinely administered intravenously. Atosiban is only approved for tocolysis up to 48 hours. With respect to several meta-analyses [31] the use of vaginal/oral progesterone for maintenance tocolysis has shown not to be associated with a significant prolongation of pregnancy and a significant reduction of neonatal morbidity in “high quality studies”. Hence, progesterone is not recommended for maintenance tocolysis by the AWMF Guideline 015-025 [7]. 93.9 % of respondents answered to perform maintenance tocolysis in patients with symptomatic placenta previa and amniotic sac prolapse, and 46.9 % in threatened preterm birth < 29 weeks of gestation. At this point it has to be mentioned that 93.9 % of OCs stated to perform tocolysis in these cases, which would be well advised to transfer patients with threatened preterm birth to a clinic with a higher perinatal care level. According to two meta-analyses [32, 33] and one RCT [34], there is no sufficient evidence that maintenance tocolysis leads to prolongation of pregnancy and improves perinatal outcomes in women with symptomatic placenta previa. However, in two of the analyses there is no information about gestational age at study entry [32, 33]. There is no RCT evaluating maintenance tocolysis in women with amniotic sac prolapse. Finally, two meta-analyses came to the conclusion that there is no evidence for the effectiveness of tocolytic treatment in women with threatened extremely preterm birth [35, 36]. Hence, maintenance tocolysis in these patients may be a case-by-case decision.

In women with PPROM the use of tocolytic agents is still a matter of debate; 96.3 % of the Austrian obstetric units stated to perform tocolysis in patients with PPROM, among these 65.4 % to complete a full course of ACS. Similar results were shown in the German survey [16]. However, several guidelines [7, 17, 20] do not recommend tocolysis in patients with PPROM based on a meta-analysis in 2014 [37] and two prospective cohort studies [10, 38]. The AWMF Guideline 015-025 stated that tocolysis in women with PPROM may only be an option to complete a full course of ACS in terms of a case-by-case decision (expert opinion) [7]. In our survey we did not collect any information about the upper gestational age limit for tocolysis in PPROM.

Betamimetics are the tocolytics with the highest rate of maternal and fetal side effects [6]. Hence, it was not surprising that 48.1 % of respondents had observed cardiac arrhythmia and 33.3 % pulmonary edema related to the use of hexoprenaline. In the German survey 70 % of respondents reported on severe side effects in association with the use of fenoterol.

Severe hypotension, significant tachycardia and pulmonary edema are dose-dependent side effects of nifedipine and were reported in a range of 0.9 % to 1.9 % [39, 40]. These severe side effects had been observed by 9.3 % of the respondents which was similar to the results of the German survey [12]. According to a recent meta-analysis, atosiban is the tocolytic agent with the lowest rate of maternal and fetal side effects [41], minor side effects such as headache or dizziness may occur, especially if the intravenous bolus is administered undiluted and rapidly [6].

There exist no evidence-based recommendations regarding measures after tocolysis at patient’s discharge from the hospital. As in the German survey close surveillance by the patient’s health care provider, followed by the daily administration of progesterone were the most important recommendations made by the obstetric units. However, there is no sufficient evidence that tocolysis with progesterone leads to prolongation of pregnancy [7]. Bedrest should be omitted, since it is associated with an increased risk of venous thromboembolism, loss of muscle mass and body weight as well as psychological sequelae such as depression and anxiety [42, 43, 44]. Nevertheless, 68.5 % of clinics stated to recommend bedrest during maintenance tocolysis.

Conclusion

Our survey agrees with others from Germany and different countries demonstrating considerable discrepancies between guideline recommendations and daily clinical practice. In this context, it should be considered that only a minority of guideline recommendations are based on high levels of evidence due to the lack of sufficient data from RCTs. Nevertheless, if obstetricians decide not to adhere to national guideline recommendations, they are at least well advised to obtain written informed consent.

It is mandatory to improve obstetrician’s low adherence to guidelines, e.g. by early access, improved dissemination, key messages with presentation of evidence levels, decision trees to improve applicability of the messages and regular external audits of PNCs. However, in some special cases one will have to choose an individual approach.

Regular national surveys are also mandatory to reveal faults in obstetrician’s adherence to national guidelines and to develop novel approaches in this issue for improving maternal health care.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

N/A.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributors' Statement

S. Enengl: protocol development, data management, manuscript writing. The present work was performed in fulfillment of the requirements for obtaining the degree "Dr. med." W. Rath: protocol development, manuscript editing; S. Kehl: protocol development, data management, manuscript editing; P. Oppelt: manuscript editing; A. Mayr: statistical analysis; A. Stroemer: statistical analysis; T. Eichinger: data management; J. Lastinger: data management; P. Stelzl: protocol development, data management, manuscript editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Goldenberg RL, Culhane JF, Iams JD et al. Epidemiology and causes of preterm birth. Lancet 2008; 371: 75–84. DOI: 10.1016/S0140-6736(08)60074-4

[2] Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science 2014; 345: 760–765. DOI: 10.1126/science.1251816

[3] Institut für klinische Epidemiologie, Teil des Landesinstituts für Integrierte Versorgung Tirol. Geburtenregister Österreich. Bericht über die Geburtshilfe in Österreich 2022. Innsbruck: Landesinstitut für Integrierte Versorgung Tirol; 2022.

[4] Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006; 19: 773–782. DOI: 10.1080/14767050600965882

[5] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269. DOI: 10.1016/S0140-6736(08)60136-1

[6] Rath W, Kehl S. Acute Tocolysis – a Critical Analysis of Evidence-Based Data. Geburtshilfe Frauenheilkd 2018; 78: 1245–1255. DOI: 10.1055/a-0717-5329

[7] Berger R, Abele H, Bahlmann F et al. [Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) – Part 2 with Recommendations on the Tertiary Prevention of Preterm Birth and the Management of Preterm Premature Rupture of Membranes]. Z Geburtshilfe Neonatol 2019; 223: 373–394. DOI: 10.1055/a-1008-8730

[8] Anonymous. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol 2021; 138: e65–e90. DOI: 10.1097/AOG.0000000000004479

[9] Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2018(11): CD012505. DOI: 10.1002/14651858.CD012505.pub2

[10] van Winden TMS, Roos C, Nijman TAJ et al. Tocolysis compared with no tocolysis in women with threatened preterm birth and ruptured membranes: A propensity score analysis. Eur J Obstet Gynecol Reprod Biol 2020; 255: 67–73. DOI: 10.1016/j.ejogrb.2020.10.015

[11] Nazifovic E, Husslein H, Lakovschek I et al. Differences between evidence-based recommendations and actual clinical practice regarding tocolysis: a prospective multicenter registry study. BMC Pregnancy Childbirth 2018; 18: 446. DOI: 10.1186/s12884-018-2078-5

[12] Stelzl P, Kehl S, Oppelt P et al. Do obstetric units adhere to the evidence-based national guideline? A Germany-wide survey on the current practice of initial tocolysis. Eur J Obstet Gynecol Reprod Biol 2022; 270: 133–138. DOI: 10.1016/j.ejogrb.2022.01.006

[13] Fox NS, Gelber SE, Kalish RB et al. Contemporary practice patterns and beliefs regarding tocolysis among u.s. Maternal-fetal medicine specialists. Obstet Gynecol 2008; 112: 42–47. DOI: 10.1097/AOG.0b013e318176158e

[14] Rousseau A, Azria E, Baumann S et al. Do obstetricians apply the national guidelines? A vignette-based study assessing practices for the prevention of preterm birth. BJOG 2020; 127: 467–476. DOI: 10.1111/1471-0528.16039

[15] Parant O, Maillard F, Tsatsaris V et al. Management of threatened preterm delivery in France: a national practice survey (the EVAPRIMA study). BJOG 2008; 115: 1538–1546. DOI: 10.1111/j.1471-0528.2008.01929.x

[16] Stelzl P, Kehl S, Oppelt P et al. Maintenance tocolysis, tocolysis in preterm premature rupture of membranes and in cervical cerclage – a Germany-wide survey on the current practice after dissemination of the German guideline. J Perinat Med 2023; 51: 775–781. DOI: 10.1515/jpm-2022-0572

[17] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. Obstet Gynecol 2016; 128: e155–e164. DOI: 10.1097/AOG.0000000000001711

[18] World Health Organization. WHO Recommendation on Tocolytic Therapy for Improving Preterm Birth Outcomes. 2022. Accessed May 23, 2024 at: http://www.ncbi.nlm.nih.gov/books/NBK585023/

[19] Sentilhes L, Sénat MV, Ancel PY et al. Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol 2017; 210: 217–224. DOI: 10.1016/j.ejogrb.2016.12.035

[20] National Institute for Health and Care Excellence (NICE). Preterm Labour and Birth. 2022. Accessed May 23, 2024 at: http://www.ncbi.nlm.nih.gov/books/NBK553008/

[21] van Winden TMS, Nijman TAJ, Kleinrouweler CE et al. Tocolysis with nifedipine versus atosiban and perinatal outcome: an individual participant data meta-analysis. BMC Pregnancy Childbirth 2022; 22: 567. DOI: 10.1186/s12884-022-04854-1

[22] van Winden T, Klumper J, Kleinrouweler CE et al. Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial. BJOG 2020; 127: 1129–1137. DOI: 10.1111/1471-0528.16186

[23] Hanley M, Sayres L, Reiff ES et al. Tocolysis: A Review of the Literature. Obstet Gynecol Surv 2019; 74: 50–55. DOI: 10.1097/OGX.0000000000000635

[24] Pinto Cardoso G, Houivet E, Marchand-Martin L et al. Association of Intraventricular Hemorrhage and Death With Tocolytic Exposure in Preterm Infants. JAMA Netw Open 2018; 1: e182355. DOI: 10.1001/jamanetworkopen.2018.2355

[25] van Vliet EOG, Nijman TAJ, Schuit E et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. Lancet 2016; 387: 2117–2124. DOI: 10.1016/S0140-6736(16)00548-1

[26] Di Renzo GC, Cabero Roura L, Facchinetti F et al. Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine. J Matern Fetal Neonatal Med 2017; 30: 2011–2030. DOI: 10.1080/14767058.2017.1323860

[27] Stelzl P, Kehl S, Rath W. Maintenance tocolysis: a reappraisal of clinical evidence. Arch Gynecol Obstet 2019; 300: 1189–1199. DOI: 10.1007/s00404-019-05313-7

[28] Dehaene I, Bergman L, Turtiainen P et al. Maintaining and repeating tocolysis: A reflection on evidence. Semin Perinatol 2017; 41: 468–476. DOI: 10.1053/j.semperi.2017.08.005

[29] van Vliet E, Dijkema GH, Schuit E et al. Nifedipine maintenance tocolysis and perinatal outcome: an individual participant data meta-analysis. BJOG 2016; 123: 1753–1760. DOI: 10.1111/1471-0528.14249

[30] Valenzuela GJ, Sanchez-Ramos L, Romero R et al. Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. The Atosiban PTL-098 Study Group. Am J Obstet Gynecol 2000; 182: 1184–1190. DOI: 10.1067/mob.2000.105816

[31] Rath W, Kuon RJ. Progesterone – Effective for Tocolysis and Maintenance Treatment After Arrested Preterm Labour?: Critical Analysis of the Evidence. Geburtshilfe Frauenheilkd 2019; 79: 834–843. DOI: 10.1055/a-0829-3992

[32] Bose DA, Assel BG, Hill JB et al. Maintenance tocolytics for preterm symptomatic placenta previa: a review. Am J Perinatol 2011; 28: 45–50. DOI: 10.1055/s-0030-1262510

[33] Morfaw F, Fundoh M, Bartoszko J et al. Using tocolysis in pregnant women with symptomatic placenta praevia does not significantly improve prenatal, perinatal, neonatal and maternal outcomes: a systematic review and meta-analysis. Syst Rev 2018; 7: 249. DOI: 10.1186/s13643-018-0923-2

[34] Verspyck E, de Vienne C, Muszynski C et al. Maintenance nifedipine therapy for preterm symptomatic placenta previa: A randomized, multicenter, double-blind, placebo-controlled trial. PloS One 2017; 12: e0173717. DOI: 10.1371/journal.pone.0173717

[35] Miyazaki C, Moreno Garcia R, Ota E et al. Tocolysis for inhibiting preterm birth in extremely preterm birth, multiple gestations and in growth-restricted fetuses: a systematic review and meta-analysis. Reprod Health 2016; 13: 4. DOI: 10.1186/s12978-015-0115-7

[36] Yamaji N, Suzuki H, Saito K et al. Tocolytic Therapy Inhibiting Preterm Birth in High-Risk Populations: A Systematic Review and Meta-Analysis. Children (Basel) 2023; 10: 443. DOI: 10.3390/children10030443

[37] Mackeen AD, Seibel-Seamon J, Muhammad J et al. Tocolytics for preterm premature rupture of membranes. Cochrane Database Syst Rev 2014(2): CD007062. DOI: 10.1002/14651858.CD007062.pub3

[38] Lorthe E, Goffinet F, Marret S et al. Tocolysis after preterm premature rupture of membranes and neonatal outcome: a propensity-score analysis. Am J Obstet Gynecol 2017; 217: 212.e1–212.e12. DOI: 10.1016/j.ajog.2017.04.015

[39] Clouqueur E, Gautier S, Vaast P et al. [Adverse effects of calcium channels blockers used as tocolytic treatment]. J Gynecol Obstet Biol Reprod (Paris) 2015; 44: 341–356. DOI: 10.1016/j.jgyn.2014.12.012

[40] de Heus R, Mol BW, Erwich JJHM et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ 2009; 338: b744. DOI: 10.1136/bmj.b744

[41] Wilson A, Hodgetts-Morton VA, Marson EJ et al. Tocolytics for delaying preterm birth: a network meta-analysis (0924). Cochrane Database Syst Rev 2022(8): CD014978. DOI: 10.1002/14651858.CD014978.pub2

[42] da Silva Lopes K, Takemoto Y, Ota E et al. Bed rest with and without hospitalisation in multiple pregnancy for improving perinatal outcomes. Cochrane Database Syst Rev 2017(3): CD012031. DOI: 10.1002/14651858.CD012031.pub2

[43] Sosa CG, Althabe F, Belizán JM et al. Bed rest in singleton pregnancies for preventing preterm birth. Cochrane Database Syst Rev 2015; 2015: CD003581. DOI: 10.1002/14651858.CD003581.pub3

[44] McCarty-Singleton S, Sciscione AC. Maternal activity restriction in pregnancy and the prevention of preterm birth: an evidence-based review. Clin Obstet Gynecol 2014; 57: 616–627. DOI: 10.1097/GRF.0000000000000048