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Off-label use of misoprostol for labor induction in Germany: a national survey

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ABSTRACT

Objective: Misoprostol is safe and effective for labor induction in viable pregnancies. Little is known about the prevalence of off-label use of misoprostol, and the reasons for using or not using misoprostol for labor induction. As such, a national survey was conducted in Germany to assess reliable data about the use of misoprostol in clinical practice.
Study design: A prospective study was performed in 2013 using a standardized survey questionnaire. All registered departments of obstetrics and gynecology in Germany were targeted.
Results: Out of 783 questionnaires, 542 (69%) were returned. Three hundred and fifty-five (66%) respondents reported that they use misoprostol for labor induction in viable term pregnancies, and 183 (34%) respondents reported that they never use misoprostol for this indication. The most common reasons given for using misoprostol in labor induction were: effectiveness (40%), good patient acceptance (35%), established/well proven in clinical practice (35%) and cost-effectiveness (32%). The most common reasons given for not using misoprostol were lack of licence (off-label use, 69%) and uncertainty of the legal situation (27%).
Conclusion: Although misoprostol is not licensed in Germany for obstetric indications, the vast majority of respondents (66%) reported that they use misoprostol for labor induction. The main reasons for not using misoprostol for labor induction in Germany are legal concerns rather than lack of scientific evidence. Cost-effective medications with evidence-based effectiveness and safety should be supported by a clear statement from national medical societies.

Introduction

Misoprostol, a prostaglandin E_1 analog, was initially approved in 1985 for the treatment of gastric ulcers, and is now available in more than 80 countries [1,2]. The effect of prostaglandins on uterine contractility has been known for over 50 years [3], and since the 1990s, a considerable amount of evidence has been obtained from randomized controlled trials showing that misoprostol is safe and effective for labor induction in viable pregnancies [4–8].

There is a growing body of evidence that low-dose misoprostol, administered orally or vaginally, is more effective [5,6,9–12] or at least as effective [13–15] as vaginal dinoprostone. Misoprostol has several advantages over commercially available natural prostaglandin E_2 (PGE_2) preparations: it can be used orally, is absorbed rapidly, has little effect on the bronchi or blood vessels, can be stored at room temperature, and is inexpensive [2].

The World Health Organization (WHO) has endorsed the important role of misoprostol by including it in the WHO model list of essential medicines for obstetric indications [16]. The recently published WHO guideline gives detailed recommendations on the use of misoprostol for obstetric and gynecologic indications [7]. The American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynecologists of Canada also recommend misoprostol as a safe and effective method for labor induction [17,18].

Debates over misoprostol have intensified in recent years; at the heart of the discussion is the role of drug licensing [2]. The manufacturer of the original preparation of misoprostol (®Cytotec; Pfizer Inc., New York, USA) has not, to date, sought approval for the agent for obstetric indications. In Europe and most other countries, misoprostol continues to be used off-label for obstetric indications, and the manufacturer has even advised obstetricians

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against its unlicensed use in pregnancy [19]. Despite off-label use and related problems, 78% of obstetricians/gynecologists in Switzerland favor the use of misoprostol for labor induction [20]. A few licensed misoprostol preparations for labor induction have been introduced to the market, mainly outside Europe (e.g. Isovent in Bangladesh). In addition, a new 200-μg misoprostol vaginal insert for labor induction has been developed and compared with a 10-mg dinoprostone vaginal insert in a phase III, double-blind, multicenter study [21]. Following favorable results (in terms of the median time to vaginal delivery) for misoprostol, the 200-μg misoprostol vaginal insert was approved for labor induction in the European Decentralized Procedure, involving 29 member states of the European Economic Area, one of which is Germany.

As little is known about the frequency of off-label use of misoprostol in Germany, and the reasons for using or not using misoprostol for labor induction, a national survey was conducted to obtain reliable data on the use of misoprostol in clinical practice.

Materials and methods

In 2013, a prospective study was conducted using a standardized survey questionnaire. All registered departments of obstetrics and gynecology in Germany were targeted. The head of each department received the questionnaire by regular mail, together with a covering letter explaining the aim and design of the study. The survey was undertaken anonymously, and a single reminder letter, including another copy of the questionnaire, was sent 3 weeks after the first return deadline. The study was supported by the German Society of Obstetrics and Gynaecology (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, DGGG). No personal data were collected in this study.

The questionnaire asked four questions regarding structural aspects of the department: annual birth rate, number of team members, specialists in obstetrics and perinatal care, and level of perinatal care. There are four different levels of perinatal care in Germany, each of which is defined by the medical expertise provided. Level I clinics are equipped with staff and infrastructure appropriate for managing any pregnancy, especially high-risk pregnancies, and very premature infants at the limit of viability. Level II clinics are equipped with staff and infrastructure appropriate for taking care of neonates of >29 + 1 gestational weeks, Level III clinics have facilities for neonates of >32 + 0 gestational weeks, and Level IV clinics include obstetric departments for low-risk pregnancies of >36 + 0 gestational weeks.

The remaining questions addressed labor induction in general and the reasons for use or non-use of misoprostol. The questions were either multiple choice or open ended.

After the completed questionnaires had been received, the data were compiled electronically. Statistical analysis included descriptive analysis and comparisons between groups. *p*-Values were calculated using Pearson's Chi-squared test, and $p < 0.05$ was considered to indicate significance.

Results

In total, 542 out of 783 questionnaires were returned (69%). As expected, the majority of the respondents were obstetric clinics (Level IV) appropriate for low-risk pregnancies (51%), followed by Level I perinatal centers (in the German classification system; 26%). The level of care was not specified in <1% of the responses. In total, 355 (66%) respondents stated that they use misoprostol for labor induction in viable term pregnancies, and 183 (34%) respondents stated that they never use misoprostol for this indication. There were no significant differences between the highest and the lowest levels of care with regard to use of misoprostol (69% vs 66%; $p > 0.05$) (Fig. 1).

The mean labor induction rate (all modes of deliveries) in hospitals that use misoprostol was 21%, compared with 19% in hospitals that do not use misoprostol; no significant differences were found between the different levels of care. Hospitals with a high labor induction rate (≥30%) reported the use of misoprostol significantly more often than hospitals with induction rates <30% ($p = 0.01$) (Fig. 2).

Hospitals that use misoprostol were significantly more likely to report the existence of established standards for labor induction than hospitals that do not use misoprostol (94% vs 89%; $p = 0.013$) (Fig. 3).

Use of misoprostol was reported more often in hospitals with annual birth rates of >1500 compared with hospitals with annual birth rates of <500 (74% vs 62%, $p = 0.069$) (Fig. 4).

Thirty-four percent of the respondents agreed that there was a need for a supportive statement from the DGGG concerning the off-label use of common drugs (e.g. misoprostol, indomethacin, nifedipine), while 5% of the respondents disagreed; 42% of the respondents stated that they would most likely change their practices with regard to the use of off-label drugs in pregnant women if this was supported by the DGGG.

Hospitals that use misoprostol for labor induction

Most respondents (94%) stated that they prefer oral administration of misoprostol, while 6% prefer the intravaginal route. Ninety-eight percent of the respondents that favor oral administration prefer to give patients a tablet, with 1.5% using the sublingual route and only 0.5% administering the tablet in sterile water. There were almost no differences between the different levels of care.

Ninety-nine percent of the hospitals that use misoprostol for labor induction stated that they inform patients that this is an off-label use. Written consent is mainly obtained using locally developed forms (88%) or commercially available forms (6.5%); 5.5% of the hospitals stated that they only inform patients verbally about the off-label use of misoprostol.

The most common reasons given for use of misoprostol for labor induction were: effectiveness (40%), good patient acceptance (35%), established/well proven in clinical practice (35%) and cost-effectiveness (32%). The availability of recommendations from

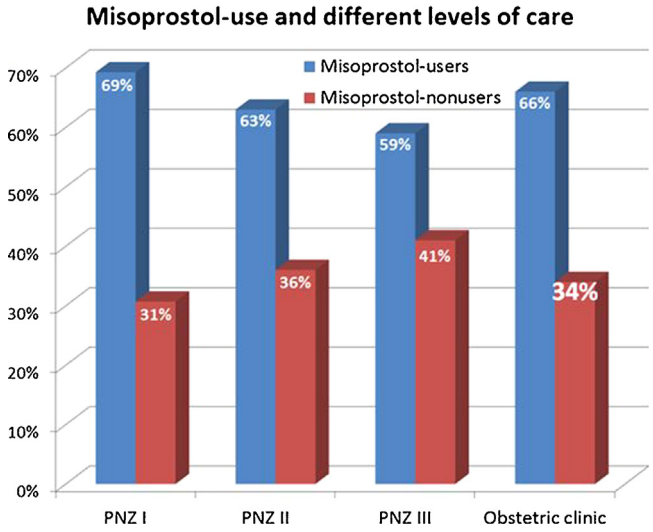

Fig. 1. Use of misoprostol for labor induction by level of care. No significant difference was found between use and non-use of misoprostol. PNZ, perinatal center.