BMJ Open

Quality assessment of patient leaflets on misoprostol-induced labour: does written information adhere to international standards for patient involvement and informed consent?

Jette Aaroe Clausen,[1] Mette Juhl,[1,2] Eva Rydahl[1]

To cite: Clausen JA, Juhl M, Rydahl E. Quality assessment of patient leaflets on misoprostol-induced labour: does written information adhere to international standards for patient involvement and informed consent?. *BMJ Open* 2016;**6**:e011333. doi:10.1136/bmjopen-2016-011333

▸ Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-011333).

Received 29 January 2016
Revised 21 April 2016
Accepted 6 May 2016

[1]Midwifery Department, Metropolitan University College, Copenhagen, Denmark
[2]Department Public Health, University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Jette Aaroe Clausen; jecl@phmetropol.dk

ABSTRACT

Objectives: The need for thorough patient information is increasing as maternity care becomes more medicalised. The aim was to assess the quality of written patient information on labour induction. In most Danish hospitals, misoprostol is the first-choice drug for induction in low-risk pregnancies. Misoprostol has been associated with adverse side effects and severe outcomes for mother and child and is not registered for obstetric use in Denmark.

Setting: Secondary care hospitals in Denmark.

Data: Patient information leaflets from all hospitals that used misoprostol as an induction agent by June 2015 (N=13).

Design: Patient leaflets were evaluated according to a validated scoring tool (International Patient Decision Aid Standards instrument, IPDAS), core elements in the Danish Health Act, and items regarding off-label use and non-registered medication. Two of the authors scored all leaflets independently.

Outcome measures: Women's involvement in decision-making, information on benefits and harms associated with the treatment, other justifiable treatment options, and non-registered treatment.

Results: Generally, the hospitals scored low on the IPDAS checklist. No hospitals encouraged women to consider their preferences. Information on side effects and adverse outcomes was poorly covered and varied substantially between hospitals. Few hospitals informed about precautions regarding outpatient inductions, and none informed about the lack of evidence on the safety of this procedure. None informed that misoprostol is not registered for induction or explained the meaning of off-label use or use of non-registered medication. Elements such as interprofessional consensus, long-term experience, and health authorities' approval were used to add credibility to the use of misoprostol.

Conclusions: Central criteria for patient involvement and informed consent were not met, and the patient leaflets did not inform according to current evidence on misoprostol-induced labour. Our findings indicate that patients receive very different, sometimes contradictory, information with potential ethical implications. Concerns should be given to outpatient inductions, where precise written information is of particular importance.

Strengths and limitations of this study

- The study had updated and complete data from all Danish hospitals that performed labour induction with misoprostol by the time of data collection.
- Patient leaflets were scored independently by two of the authors.
- Patient leaflets were evaluated against a validated scoring tool and according to national legislation.
- Data included written patient information alone, and so the study cannot conclude on other aspects of patient information.

BACKGROUND

Health professionals must respect a patient's right to take decisions about own health and her right to informed consent to a proposed treatment.[1 2] Today, one in four deliveries is being induced following a rapid increase from 7% in 1997 to 25% in 2013.[3] One reason for the increase is a reduction in the accepted normal length of pregnancy from 14 to 7–10 days past due date.[4] Previously, the prostaglandin-E_2 drug, Minprostin, was the first-choice drug for labour induction. In the beginning of the 2000s, however, 50 µg Cytotec (containing the prostaglandin-E1 substance, misoprostol) was introduced as an off-label alternative, that is, misoprostol was not registered for labour induction, and Cytotec tablets were produced for peptic ulcer treatment.[5] Misoprostol was considered superior to Minprostin with regard to induction efficiency, and today misoprostol is common for induction in low-risk pregnancies in Denmark

and other countries.[6 7] Despite the widespread use of misoprostol and the dramatic increase in induced deliveries, no scientific knowledge exists on the quality of patient information regarding misoprostol-induced deliveries. Acknowledging the fact that good patient information is (almost) always required in modern healthcare, we argue below why certain circumstances highlight the urgent need for thorough information in the case of misoprostol-induced deliveries.

First, using a drug outside its registered indications is unusual when a registered drug is available. When introduced, misoprostol was not registered for labour induction in Denmark, and until 2014 local hospital pharmacies produced vaginal suppositories from Cytotec tablets. Cytotec is produced for peptic ulcer treatment, but due to its misoprostol content it also has a uterotonic effect. Following an increased control with hospital pharmacies in 2014,[8] the production of off-label misoprostol from Cytotec stopped. Some years earlier, another misoprostol product, Angusta, was introduced in Denmark. Angusta is produced in India and is not a registered drug in Europe.[9] In order to use a non-registered drug as common treatment, a compassionate user permit is required, and thus, after the first permit for Angusta was launched by the Danish Health and Medicines Authorities in 2012, 18 of the 22 Danish obstetric departments had a compassionate user permit by June 2013.[10] Such a launch of compassionate user permits to several hospitals is the first example of Danish authorities allowing the routine use of a non-registered drug in a situation where a registered drug is available. In 2011, the legal advisor to the Danish Government stated that information prior to a treatment is essential in the case of off-label medication, and that off-label treatment should only be considered when no appropriate registered alternatives exist.[11] In 2013 the Danish Health and Medicines authorities informed all Danish labour wards that health professionals' duty to inform patients about adverse side effects were sharpened if a medication is used outside its approved indications.[12] Further, patients who are offered non-registered medication encounter barriers when they search for information. Registered drugs have product information sheets with information on effects, side effects, and how to react to and report side effects. For non-registered drugs, however, no such standardised information exists. Information about product-name, active substance, and the legal status of the drug is required if patients and professionals wish to search for further information.

Second, misoprostol and other induction agents have been associated with hyperstimulation of the uterus and fetal heart rate abnormalities.[7 13] When the uterus is stimulated extensively, the oxygen flow to the placenta and fetus is decreased. Misoprostol is a highly potent drug for which adverse effects have been reported even from low doses.[7] The incidence of hyperstimulation after low-dose oral misoprostol (25 µg) induction has been reported as 1–9%.[13–15] Misoprostol has also been associated with severe side effects such as fetal death, fetal brain damage, uterine rupture/perforation, retained placenta, amniotic fluid embolism and abnormal uterine contractions,[16–20] as well as with more frequent side effects, such as hyperstimulation, impaired fetal heart rate and meconium stained amniotic water.[7 13 16 19 20] The US Food and Drug Administration (FDA) has questioned the safety of obstetric use of Cytotec.[16 21] Even so, low-dose misoprostol (<50 µg) is recommended by the Danish Society of Obstetrics and Gynaecology and the Regional Official Authorities.[22 23] The concerns raised make it crucial that patients receive information before misoprostol-induced delivery.

Third, in Denmark, labour induction often follows an outpatient procedure, even though the product information for Minprostin (the former first-choice drug) designates that treatment with medical induction agents should be monitored in a hospital setting.[24] In Norway and other countries, continuous clinical observation is mandatory throughout misoprostol treatment.[25] Also, the WHO states that induction should only be carried out when facilities for monitoring and emergency treatment for mother and child are available.[26] Misoprostol is administered up to four times a day, and it is normal Danish practice to discharge low-risk women to their own home after misoprostol application to await the establishment of regular uterine contractions or to medicate themselves at home.[6] There have, however, been reports on tetanic labour occurring in the woman's home several hours after misoprostol application, and the safety of this practice lacks evidence.[13 27] Since tetanic labour must be treated with tocolytic drugs or emergency caesarean section, and since such treatments cannot be immediately performed outside the hospital, potential health risks may be associated with the Danish practice, and the need for adequate patient information is critical.[16 17 20 24 25 28 29] According to the Regional Official Authorities, the majority of inductions in Denmark are performed in an outpatient setting,[23] and according to the Danish Society of Obstetrics and Gynaecology this is apparently without increased risks among a low-risk population.[22]

According to the WHO, treatment must not be initiated without patient consent, and expected benefits from a treatment or an intervention should outweigh its potential harm.[26] The principle of informed consent is also reflected in the Danish Health Care Act.[1] Healthcare professionals are important providers of information,[30] and information must be delivered in respect for the individual, her integrity and self- determination. These values are stipulated in the Danish Health Care Law.[1] Women today want to participate in decisions regarding interventions in their pregnancy, and thus healthcare professionals are an important source of information.[30]

We assessed the quality of patient information leaflets on labour induction according to a validated patient

decision tool,[31] and core elements on patient information in the Danish Health Act,[1] that is, (1) women's involvement in decision-making and their right to informed consent, (2) benefits and harms associated with the treatment, and (3) other justifiable treatment options including watchful waiting (defined as a regimen for monitoring fetal well-being regularly while awaiting spontaneous onset of labour). Also, specific issues related to non-registered medication were analysed.

MATERIAL AND METHODS

During calendar week 25 in 2015, we contacted the leading midwife or the midwife responsible for patient information material in all obstetric departments in Denmark (N=22) by phone to ask if they used misoprostol for labour induction. Danish hospitals use either the registered drug Minprostin (dinoprostone) or misoprostol for medical induction. We received written patient information material on labour induction from all hospitals that performed misoprostol inductions (N=13) by postal mail, email or downloaded from the internet. Five hospitals had two different leaflets, and so we received 18 leaflets. For those five hospitals, we assessed each leaflet pair as one, resulting in the assessment of 13 hospitals' written information. All leaflets were in Danish language.

We used the revised International Patient Decision Aid Standards (IPDAS) checklist together with a scoring tool developed by the Picker Institute, which had a few adaptions to the original IPDAS checklist.[32] The scoring tool comprises eight major sections (as presented in table 1) with 2–7 subitems (for the list of subitems, please refer to online supplementary table S1). Each section had a maximum score of 5 points, no matter the number of subitems, giving a total maximum of 40 points. We generated a ninth section regarding non-registered medication (as displayed in table 2), and thus our checklist had a total score of 45 points. In the new section 9, subitems 1-3 built on the Danish Health Act and the legal advisor to the Danish Government's statement regarding information and consent.[1 11] Subitems 4–7 on product name and active substance were included because such information is required if patients wish to seek further information on the medication. Subitem 8 was based on the legislation that midwives and physicians have an increased duty to report adverse side effects from non-registered drugs and from medications used on a compassionate user permit.[33]

Two of the authors, Rydahl and Clausen, made an individual scoring of all leaflets. There was a high agreement between their scorings, and smaller disagreements were resolved by discussion. For the five hospitals with two leaflets, each was assessed individually and subsequently scored as one. In case of inconsistency within a leaflet pair, the scores from the better performing leaflet were chosen. To obtain five points in a section, the leaflet should fulfil the IPDAS criteria of all subitems of the section. Scores of 4, 3 and 2 were assigned if the leaflet partially fulfilled the criteria, and 1 was given if the leaflet did not meet the criteria in any way. From this, it follows that in cases where only very sparse information was given for a section, two points were assigned. This choice was made to make a clear distinction between no information at all and touching on a subject. For example, a leaflet that mentioned trivial inconveniences (eg, stings) but did not give information on severe adverse effects was assigned two points for the section on side effects. All citations from patient leaflets represent the authors' translation. In cases of poor Danish language in the original, this was sought to be maintained in the English translation.

Since data for this study did not include information on individual subjects, no ethics approval was required.

RESULTS

Table 1 shows hospital scores according to IPDAS. Generally, the hospitals scored low with a mean hospital score of 18 (range 12–25), compared with a possible maximum of 45 points (table 1). Also, the section scores were generally low with a mean 2.0 points (range 1.2–3.3). Leaflet structure and layout were best covered in the leaflets while information on accuracy, disclosure of conflicts of interest, and information on treatment outcomes probabilities had the lowest mean scores.

Decision-making

While the decision-making process of a patient is inherited in the IPDAS checklist (ie, table 1, section 5), it is also specified as one of the core elements in the Danish Health Act and thus addressed separately in this paper. Overall, women's involvement in the decision on labour induction and on methods for induction was not, or only sparsely, supported in the patient information leaflets. One leaflet explicated that the woman and her partner make an agreement with the midwife whether they prefer to have the labour induced or to await spontaneous onset of labour, and, if the woman does not wish to get induced, close surveillance of the child will be offered (Herlev). Six of the 13 hospitals vaguely touched on the decision-making process, and phrases such as 'we recommend' or 'we offer' were commonly used and always in favour of induction. An interaction between the obstetrician or midwife and the woman was indicated in phrases such as: 'Your doctor and midwife will inform you, why we recommend induction of labour' (Odense/Svendborg), or 'Induction of labour is decided between you and a midwife or one of the ward's obstetricians' (Hvidovre). Three leaflets did not mention the decision-making process. The remaining two addressed the decision about induction like this: 'The decision to induce labour is always medically justified on the basis of either the mother's or the child's condition' (Viborg), and 'basically there are two options: 1: prostaglandins (a pill you eat); 2: induction

Table 1 Hospital scores from patient information leaflets on labour induction according to the revised International Patient Decision Aid Standards instrument (IPDAS) checklist

Sections* Leaflet publication date	Bornholm February 2012	Herning/ Holstebro† September 2012	Herlev† September 2014	Hillerød June 2015	Horsens May 2013	Hvidovre† December 2014	Odense/ Svendborg May 2015	Randers February 2015	Rigshospitalet March 2015	Roskilde† December 2014	Skejby March 2015	Thy-Mors October 2014	Viborg† July 2013	Mean score
Does the information leaflet…														
(1) Start with a clear statement of aims?	2	2	2	2	2	2	2	2	2	2	2	2	2	2.0
(2) Provide unbiased and detailed information about options?	2	3	2	2	2	2	3	2	4	2	2	2	2	2.3
(3) Present probabilities of outcomes in an understandable way?	1	2	1	1	1	1	3	1	2	1	1	1	1	1.3
(4) Contain accurate information?	1	2	1	1	1	1	2	1	2	1	1	1	1	1.2
(5) Help patients to make appropriate decisions?	2	2	3	2	1	2	3	1	4	2	1	1	1	1.9
(6) Disclose conflicts of interest?	1	1	1	1	1	1	1	1	1	1	4	1	1	1.2
(7) Have a clear structure and layout?	1	3	3	2	5	4	4	2	5	3	5	2	4	3.3
(8) Help the reader to judge its reliability?	2	2	3	3	3	3	1	3	3	3	3	1	3	2.5
(9) Provide unbiased information about the use of non-registered drugs?	2	2	2	2	2	2	3	2	2	2	2	1	2	2.0
Total score‡	14	19	18	16	18	18	22	15	25	17	21	12	17	17.9

All Danish obstetric departments that used an induction agent by week 25, 2015. N=13.
*Each section (1–8) is described in more detail in online supplementary table S1. Section 9 is described in more detail in table 2.
†These hospitals had two leaflets on labour induction. The two leaflets were scored together as one package.
‡Possible minimum=9. Possible maximum=45.

Table 2 Hospital scores on specific issues related to non-registered medication from patient information leaflets on labour induction

Section 9 subitems	Bornholm	Herning/ Holstebro*	Herlev*	Hillerød	Horsens	Hvidovre*	Odense/ Svendborg	Randers	Rigshospitalet	Roskilde*	Skejby	Thy-Mors	Viborg*	Total
Does the information leaflet…														
(1) State that the use of misoprostol is off-label/ non-registered?	–	–	–	–	–	–	–	–	–	–	–	–	–	0
(2) Explain what it means to use medication off-label/ non-registered?	–	–	–	–	–	–	–	–	–	–	–	–	–	0
(3) State if there are other relevant and registered alternatives?	–	–	–	–	–	–	X	–	X	–	–	–	–	2
(4) State the name of the medical product name?	–	–	–	X	–	X	X	–	–	X	–	–	X	5
(5) State the name of the active substance?	X	X	X	–	X	X	X	–	X	X	X	–	–	9
(6) Describe route of administration?	–	–	X	–	–	X	X	X	–	X	X	X	X	8
(7) Describe dose of medication?	–	–	X	–	–	–	–	–	–	–	–	–	–	1
(8) Advise patients how to report side effects?	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Total section 9 score†	2	2	2	2	2	2	3	2	2	2	2	1	2	

All Danish obstetric departments that used misoprostol as an induction agent by week 25, 2015. N=13.
*These hospitals had two leaflets on labour induction. The two leaflets were scored together as one package.
†Possible minimum=1. Possible maximum=5. Note that the total scores do not, and should not, equal the number of Xs above.

with artificial rupture of membranes (to break the water)' (Randers).

Benefits and harms

Another core element in the Danish Health Act regards information on benefits and harms of the treatment, corresponding to the IPDAS checklist, section 3 (table 1, section 3). Regarding benefits, induction was generally presented as a 'prophylactic intervention' that could prevent harm, and benefits from induction were given in all leaflets. The rationale for induction was typically phrased as 'The reason why we offer induction at this time is that some children begin to receive too little nourishment from the placenta, when they stay in the uterus this long' (Bornholm). The tone in the leaflets was generally reassuring, and many leaflets implied that induced labour is close to a non-interventional delivery, for example, 'The pills used for induction are synthetic hormone (prostaglandin), which corresponds to the hormone the body produces itself during labour' (Hvidovre) or 'Vaginal suppositories […] is the method that best resembles the normal birth's start' (Roskilde), or 'even though your contractions have been assisted […], you have as a starting point the same options […] as if your labour had started spontaneously' (Viborg).

Regarding the general side effects, six hospitals mentioned some of the following: diarrhoea, nausea, vomiting, abdominal pain, rash, headache, dizziness and fever. This list corresponds to the side effects described in the product information on Cytotec for treatment of peptic ulcers.[19]

Regarding the obstetric side effects, eight hospitals presented some information, while five did not include any information. Considerable variations were observed between the hospitals that presented obstetric side effects, both in terms of what types of side effects were presented and whether they were described as frequent or rare. One of the most frequent adverse side effects from labour induction, hyperstimulation, was described as a side effect by less than half of the hospitals. The hospitals used various terms, such as over-stimulation, frequent contractions, frequent contractions without pauses, too frequent contractions, tetanic labour or 'an unusually strong reaction to the treatment resulting in a too fast progress of delivery'. One hospital described hyperstimulation as a risk only if the medication was administered incorrectly: 'If you have a too large dose of the drug, or if the tablets are taken with too short time intervals, frequent and strong contractions can occur, which can be disadvantageous to your child.' (Viborg). In some cases, 'powerful labour work' or 'very fast delivery' were used as an implicit indication of risk.

Adverse fetal outcome was mentioned in four of the leaflets. Fetal death was mentioned by one hospital as a rare risk (Hvidovre). Three hospitals gave vague indications of fetal asphyxia, for example, 'the child can be momentarily stressed after birth' (Odense/Svendborg, Rigshospitalet), or 'use of Angusta-tablets (Misoprostol) and other induction medications […] can in rare occasions affect the child' (Roskilde). Two hospitals informed about an increased risk of additional interventions, such as medical augmentation of labour, epidural anaesthesia or instrumental delivery, while one hospital stated that labour induction was not associated with an increased risk of caesarean section or instrumental delivery (Viborg).

Regarding disadvantages, longevity of labour was mentioned by six hospitals, for example: 'When a birth starts by itself, it is important to be patient, as it may take long until the contractions are effective. It is also important to be patient when labour is induced' (Randers) or 'so it is good to be patient — just like at a normal birth' (Bornholm).

It appeared from the leaflets that all hospitals performed outpatient inductions of low-risk women. Most hospitals gave some information about the timing of admission to the hospital, varying from beginning contractions/early labour (N=4), as recommended by the Danish Society of Obstetrics and Gynaecology,[22] to frequent contractions. One hospital addressed hyperstimulation thus: 'If you have very strong or frequent contractions, it is important, that you contact the midwife at once' (Bornholm). Other reasons for contacting the labour ward included non-specified contractions (N=6), loss of amniotic fluid (N=6), bleeding (N=3), pain (N=2), or less fetal movements (N=1). Four hospitals did not provide any information on when to contact the labour ward. One hospital offered the woman the opportunity to remain hospitalised if she felt unsafe about the outpatient setting (Hillerød). No hospitals informed about the need for continuous monitoring or the lack of evidence for ambulant induction.

Regarding information on probabilities of outcomes, one hospital provided probability scores according to the risks and benefits of induction: 'If 1000 pregnant women in week 41+3 choose to await spontaneous labour, at least 999 babies will still be well in week 41+5. At this time, we recommend induction' (Herning/Holstebro). Two hospitals quantified the risk of hyperstimulation after induction as 'a small risk (less than 1 in 100)' (Odense/Svendborg, Rigshospitalet), or 'utmost rare (less than 1 in 10 000)' (Hvidovre), which is a difference in probabilities by a factor of 100.

Other justifiable treatment options

The IPDAS checklist addresses information about options in section 2 (table 1, section 2), which is a third core element in the Danish Health Act. In our data, watchful waiting was mentioned as a possible alternative to induction by one hospital: 'If you do not wish to have your labour induced, you will be offered examination and consultation about how the rest of the pregnancy can continue' (Odense/Svendborg). Two others gave the impression of watchful waiting as an option, for example: 'If you choose not to be induced at week 41+5, you will be offered close monitoring. We cannot

recommend any women to continue pregnancy beyond 42 completed weeks of gestation' (Rigshospitalet), or 'at this consultation [41+3] the midwife will clarify with you and your partner, whether you wish to have the labour induced, or if you would rather wait a couple of days to await spontaneous labour' (Herning/Holstebro). In the latter example, the woman was given the opportunity of a maximum of another 2 days before induction.

Issues regarding non-registered drugs

Table 2 shows hospital scores on specific issues related to non-registered drugs. Overall, the hospital scores were low, that is, an average of 2.0 of the 5 possible points (table 2). The best covered subitems concerned information on the active substance misoprostol and on the route of administration (oral/vaginal). None of the hospitals informed that misoprostol is not registered for labour induction in Denmark or explained the meaning of off-label use or use of non-registered medication. Two hospitals addressed the topic indirectly by saying that misoprostol had been developed for another purpose or by mentioning the compassionate user permit for Angusta issued by the Danish Health Authorities, yet without explaining the meaning of such a permit. A few others added credibility to the use of misoprostol in phrases such as: '[…] misoprostol, is developed for another medical purpose, but has for more than 10 years been approved by the Danish Health Authorities for labour induction' (Odense/Svendborg), or 'misoprostol has been used for labour induction for many years, both in Denmark and in larger parts of the world' (Rigshospitalet), or by referring to a consensus between midwives and obstetricians on the choice of treatment.

Even though several hospitals gave information about the former first-choice drug, Minprostin, only two presented this as optional for 'all' women. One of them said: 'if you do not wish to be treated with Angusta, we can instead induce labour with Minprostin…' (Odense/Svendborg). In the other, the message was kind of hidden, that is, in the leaflet section on side effects, it was mentioned that Minprostin vagitories could be an alternative to misoprostol, and that Minprostin has the same side effects as misoprostol 'but [with Minprostin®] there are more deliveries that end in a caesarean section' (Rigshospitalet). Otherwise, Minprostin was mentioned to describe the induction agent for certain conditions (eg, twin pregnancy or previous caesarean section). Nine hospitals gave the name of the active substance misoprostol, and six gave the medical product name, that is, Angusta (N=5) and Cytotec (N=1). Most hospitals mentioned prostaglandins in general terms and explained its cervical ripening effect. Most hospitals also informed about the route of administration (ie, oral or vaginally). About half of the hospitals informed about the course of treatment during one or more days of induction, or they informed about the number of tablets, capsules, etc, at different stages of treatment. Such detailed information was, however, presented without any information on drug dose, for example: 'the next day you will be treated with misoprostol again, but now in double dose' (Herning/Holstebro). One hospital informed about the drug dose (25 µg) (Herlev). No hospitals advised patients on how to report side effects from the treatment.

DISCUSSION

This survey showed that written information about induction of labour to pregnant women by Danish hospitals lacked several important criteria for patient involvement and informed consent, and that the written information varied considerably between hospitals.

According to the IPDAS scoring tool, several elements should be included in order to provide unbiased information. We found that information on health condition was addressed by pointing out the risk for the fetus (in carrying on the pregnancy), that the leaflets did not describe the natural course of pregnancy without treatment, that only one hospital informed about watchful waiting as a genuine alternative option to induction, that benefits of options were given only for induction and not for alternative options, such as watchful waiting with the possibility of spontaneous onset of labour, that risks of options (harms, side effects, disadvantages) were sparsely or inadequately communicated, that no hospital informed about the uncertainty around current evidence, and finally, that most hospitals described procedures on the course of treatment. Hence, overall, the leaflets provided information in favour of induction and of misoprostol.

These findings were further supported by the tone and wording in the text. For example, frequently used terms such as 'we recommend' or 'we offer you' indicate a paternalistic attitude, which is not conducive to patient participation in decision-making. Also, terms associated with a natural or normal birth are used in more of the leaflets, eg, 'The pills used for induction are synthetic hormone (prostaglandin), which corresponds to the hormone the body produces itself during labour' (Hvidovre) or 'Vaginal suppositories […] is the method that best resembles the normal birth's start' (Roskilde), or 'even though your contractions have been assisted […], you have as a starting point the same options […] as if your labour had started spontaneously' (Viborg). Such terms, can be used to downgrade the understanding of labour induction as a medical intervention, since they usually relate to non-interventional childbirth.[34] Regarding the unorthodox use of misoprostol for labour induction, trustworthy elements such as interprofessional consensus, long-term experience or a reference to national health authorities' approval were used to add credibility to the practice. If a hospital offers a woman the opportunity to wait another 2 days before induction, the woman can feel that she has a choice, but both options are still within the Danish Society of Obstetrics

and Gynaecology's recommended time frame of pregnancy termination before 42 gestational weeks.[4]

Unlicensed misoprostol is mentioned in the WHO essential drug list[35] and is recommended for induction of labor in under-resourced settings.[26] According to the legal advisor to the Danish government, a stricter requirement for patient information applies to off-label medications, that is, medication used outside its indication.[5] When the peptic ulcer-registered medication, Cytotec, is used as an induction agent, this is an example of off-label use. This is different to Angusta, which was introduced in Danish obstetrics after a period of off-label use of Cytotec. Since Angusta is not registered as a medication in Europe, the term 'off-label' does not apply to its use in Denmark. Angusta has not been tested in any published trials, and the procedure that Danish hospitals have compassionate user permits for Angusta is an extreme and unusual case. Hence, it is unlikely that the legal advisor's stricter patient information requirements for off-label use should not apply to women who are offered Angusta, that is, a non-registered drug. The one leaflet that informed about the compassionate user permit for Angusta issued by the Danish Health Authorities gave confusing information. The one leaflet that mentioned the compassionate user permit for Angusta issued by the Danish Health Authorities gave confusing information. Hence, the term compassionate user permit was mentioned, but no explanation as to the meaning and purpose of such permit was given. The compassionate user permit allows a hospital to use Angusta in cases where there is a lack of other suitable and registered drugs available,[11] and when, in the case of labour induction, for example, Minprostin is available, it can be argued that the routine use of Angusta in Danish hospitals does not apply to the formal conditions for a compassionate user permit.

Information on side effects from the treatment was highly inconsistent, showed large variations between hospitals, and sometimes required substantial professional or linguistic skills to disentangle. For example, the fact that 'strong contractions' in one leaflet should be understood as a sign of danger was apparent only because this was placed in the side effect section. In a common understanding, strong contractions might be understood as a part of the normal course of labour, while specialists will know that, in this context, it may refer to hyperstimulation or tetanic labour. During analysis, it became obvious that more hospitals had included standard side effect information (from eg, Cytotec) directly in the leaflets, for example, to present abdominal pain as a side effect seems meaningless in relation to induction of labour. The majority of leaflets did not provide any information on the risk of additional interventions after induction, such as medical augmentation of labour, epidural, instrumental delivery or caesarean section. Such interventions are all relevant to consider prior to treatment.

Probabilities of hyperstimulation after misoprostol induction were presented by three hospitals with risk estimates from 'a small risk less than 1 in 100' to 'an extremely rare event less than 1 in 10 000'. The outcome probabilities presented by three hospitals are without references. These probabilities are lower than those reported by The Cochrane Collaboration and differ from the Cytotec product information.[7 13 19] Cochrane reports 1–9% hyperstimulation from low dose oral misoprostol trials, while the Cytotec product information reports 0.1–1% uterine tetany and 'un-known incidence' of uterine rupture, bleeding, emboli and abnormal uterine contractions.[13 19]

It is crucial that women receive information on when to contact the labour ward, how to react appropriately to adverse effects, and the lack of evidence on the safety of this procedure. The Danish Society of Obstetrics and Gynaecology recommends fetal surveillance early in labour after misoprostol induction.[22] To make this possible, the woman must arrive at the hospital in early labour, but only four leaflets gave this information in their written patient information material. Hence, it may be argued that the fact that most of the leaflets failed to give crucial information on how to react while at home during labour induction poses a risk to the mother and/or child.

While poor fetal outcome was presented as the main reason for terminating the pregnancy, it is also found to be a possible adverse effect of labour induction. From a patient perspective, the information on which to make a choice is not balanced when induction is presented as an action to prevent poor fetal outcome and, at the same time, the fetal risk associated with the intervention itself is not presented. This could be addressed by including balanced information about options and by presenting absolute risks or probabilities in the leaflets. Since emergency treatment of fetal asphyxia is not possible at home, outpatient inductions carry a special safety concern.

The strengths of the study include the use of the revised IPDAS checklist scoring tool, which is validated and has been used to evaluate patient information material in other healthcare areas,[32] and independent scoring by two of the authors. Also, patient leaflets from all relevant hospitals were included. Weaknesses include the fact that the extra section on non-registered drugs was developed for the present study and thus not tested or validated previously. Also, since the study included written patient information alone, and since the IPDAS checklist only concerns written patient information material, our results cannot conclude on other aspects of the information material and the decision-making process.[36]

In conclusion, the assessed patient information leaflets lacked several central elements of patient involvement criteria, and they presented unbalanced information on benefits versus harms. The leaflets did not inform adequately on current evidence on labour induction, including treatment options, outcome probabilities or possible risks related to non-intervention, and they did not help the women to make appropriate decisions or to

judge the material's reliability. In some cases, the leaflets might even be hazardous due to lack of crucial information. If a woman shall give informed consent on labour induction, she needs information about side effects and on the consequences of induced versus spontaneous onset of labour.

Overall, there was considerable inconsistency in the information provided across hospitals. Women admitted to different hospitals will thus receive different information, which has ethical implications.

Producing appropriate written patient information is not an easy task, and the challenge is further increased when a non-registered drug is suggested as standard treatment, as is the case with Angusta. The authors encourage clinicians and researchers to work together in the development of written patient information material, and recommend the use of contemporary decision aid tools.

Contributors JAC and ER conceptualised the idea of the study. JAC, ER and MJ contributed considerably to the design of the work; and to the acquisition, analysis and interpretation of the data. They also contributed considerably to the drafting and revision of the paper; and to important intellectual discussions forming the final submitted version. All authors have approved the submitted version and agree to be accountable for all aspects of the work.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data for the study consist of written patient information leaflets. The material can be requested by contacting the authors, if not available from the relevant hospitals.

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