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Misoprostol use under routine conditions for termination of pregnancies with intrauterine fetal death☆

Maria Isabel do Nascimento[a,*], *Alfredo de Almeida Cunha*[b], *Sandra Regina dos Santos Muri Oliveira*[a], *Glaucimara Gonzaga Nunes*[a], *Felipe Silva Alvarez*[a], *Eduardo Loyola Villas Bôas*[a]

[a] *Hospital Geral de Nova Iguaçu, Nova Iguaçu, RJ, Brazil*
[b] *Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*

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ABSTRACT

Objective: To analyze the misoprostol use in pregnancies with intrauterine fetal death (IUFD), considering mode of delivery and induction-delivery interval.
Methods: Descriptive study including 171 pregnant women with IUFD, in the second or third trimester, submitted to labor induction with vaginal misoprostol and/or induction/augmentation with intravenous oxytocin, from 2005 to 2008, at a teaching-hospital of the Brazilian Unified Health System (Sistema Único de Saúde - SUS).
Results: Misoprostol alone (treatment A), misoprostol plus oxytocin (treatment B), and oxytocin alone (treatment C) were administered in 9.3%, 19.9%, and 70.8% of the cases, respectively. One-third of pregnancies were less than 28 weeks, and 2.9% required a caesarean section. The percentage of vaginal delivery in treatments A and B combined (98.0%) was similar to treatment C (96.7%). The mean induction-delivery interval was 15.4 hours. Comparing multiple groups, the mean induction-delivery interval was significantly shorter in treatment A (20.1 hours) than in treatment B (33.3 hours), and was longer than in treatment C (9.7 hours). The majority (71%) of cases required a single administration of misoprostol, and the total dosage was lower in treatment A (mean: 98.4 μg) compared with treatment B (mean: 157.0 μg).
Conclusion: Misoprostol effectively contributed to delivery of IUFD by vaginal route assisted under routine conditions of a public health service in Brazil, demonstrating its importance in cases resistant to usual induction methods, and its availability in Brazilian public health services is recommended.

Uso de misoprostol na rotina para terminar gestações com feto morto

Palavras-chave:
Misoprostol

RESUMO

Objetivo: Descrever o uso de misoprostol em gestações com óbito fetal intraútero, considerando o tipo de parto e o intervalo indução-parto.

☆ Study conducted at the Obstetrics Department of Hospital Geral de Nova Iguaçu, Nova Iguaçu, RJ, Brazil.

* *Corresponding author.*
E-mail: ysamaria@uol.com.br (M.I. Nascimento).

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Ocitocina
Trabalho de parto induzido
Parto obstétrico
Óbito fetal
Feto morto

Métodos: Estudo descritivo de 171 gestantes com óbito fetal intraútero, no segundo ou terceiro trimestres, submetidas à indução do parto com misoprostol vaginal ou aceleração do parto com ocitocina parenteral, de 2005 a 2008 em um hospital-escola do Sistema Único de Saúde (SUS) do Brasil.
Resultados: Misoprostol isolado (tratamento A), misoprostol complementado pela ocitocina (tratamento B) e ocitocina isolada (tratamento C) foram administrados em 9,3%, 19,9% e 70,8% dos casos, respectivamente. Um terço das gestações estavam com menos de 28 semanas e 2,9% delas requereram operação cesariana. O percentual de parto vaginal nos tratamentos A e B combinados (98,0%) foi similar ao tratamento C (96,7%). A média do intervalo indução-parto foi menor no tratamento A (20,15 horas; DP = 15,8 horas) comparado ao tratamento B (33,31 horas; DP = 29,6 horas) e a proporção de partos pela via vaginal ocorridos dentro de 48 horas foi de 100% (tratamento A), 96,7% (tratamento B) e 96,7% (tratamento C). A maioria dos casos (71%) tratados com misoprostol requereu uma única administração da droga e a média da dosagem total foi menor no tratamento A (média 98,4 μg) comparado ao tratamento B (média: 157,0 μg).
Conclusão: Misoprostol efetivamente contribuiu para a resolução de gestações com óbito fetal intraútero, mostrando a importância de sua aplicação em casos resistentes aos métodos usuais de indução e de sua disponibilização nos serviços públicos de saúde no Brasil.

Introduction

The effectiveness of misoprostol for labor induction has been widely demonstrated by several randomized controlled trials (RCTs),[1] but the absence of its registration for obstetrical and gynecological applications remains an important problem in most countries.[2] Currently, Brazil and Peru are the only Latin-American countries to make misoprostol officially licensed for reproductive health indications. In Brazil, misoprostol is approved for vaginal use, and the preparation is indicated in cases when it is necessary to induce labor in a full-term or near full-term pregnancy, to induce labor of retained dead fetus, or in the case of legal abortions.[3]

Despite official regulation by government, the irregular supply of misoprostol is still a barrier in Brazil, which might limit its access[4] and in turn lead health professionals to make difficult choices regarding the treatments to be administered and/or opt for a suboptimal amount of misoprostol.[5] Additionally, the use of misoprostol in the presence of a previous uterine scar[6] and/or previous caesarean section increases the risk of uterine rupture.[7]

As the lack of license for certain misoprostol obstetrical indications is not a problem in Brazil, experiences other than RCT may contribute to increase the understanding of the subject, especially if the focus is on medical labor induction practiced in low-resource environments. Thus, the objective of this study was to describe the use of misoprostol in pregnancies with intrauterine fetal death (IUFD), in the second or third trimester, regarding mode of delivery and induction-delivery interval.

Methods

This was a descriptive study carried out with pregnant women with IUFD who were submitted to medical labor induction from January of 2005 to December of 2008 at a teaching hospital of the Brazilian Unified Health System (Sistema Único de Saúde – SUS).

Study population

According to the Brazilian Mortality Information System, 410 singleton gestations with dead fetuses registered at the aforementioned hospital were over 499 g birth weight and/or $\geq$ 22 weeks of gestational age, and thus were eligible for this study. Initially a total of 219 women were excluded for the following reasons: postpartum admission (15), emergency C-section (98), spontaneous deliveries (104), or use of Foley catheter followed by a C-section (2). The inclusion criteria for medical labor induction and/or augmentation with medications was fulfilled by 191 pregnant women. Of these, 20 were also excluded for the following reasons: (i) eight cases of medical induction in simultaneous use of Foley catheter method; (ii) ten cases of clinical induction initiated when the fetus was still alive (one anencephalic, one unexplained death, and eight cases of chorioamnionitis); (iii) two cases of loss of information about fetal vitality at the beginning of induction. The current study comprised 171 patients who received medical treatment for labor induction with vaginal misoprostol or labor augmentation with intravenous oxytocin infusion.

The medical treatment for labor induction or labor augmentation to terminate IUFD pregnancies is routinely performed in this hospital with misoprostol and/or oxytocin. Misoprostol is indicated for unfavorable cervix considering length, position, dilation, and station, and is exclusively administered vaginally. A favorable or mature cervix is that with 2 cm of dilation, 80%effaced, soft, and in midposition, and with a fetal occiput at −1 station, with a prognosis of vaginal delivery;[8] otherwise, the cervix is classified as immature or unfavorable. When the cervix becomes favorable, the intravenous oxytocin infusion is performed to supplement previously administered misoprostol. In contrast, oxytocin

alone is recommended for augmentation of spontaneously initiated labor or to supplement the induction with misoprostol. The oxytocin infusion is administered in 500 mL of 5% glucose, intravenously, with initial dose of 2 mIU per minute, increasing until the uterus attains a level of activity similar to the physiological.

The mode of delivery (vaginal or caesarean section) and the induction-delivery interval were the two main outcomes studied. The induction-delivery interval comprises the interval between the beginning of induction or augmentation with use of medication and the fetus expulsion. This interval was measured in hours, and evaluated both as continuous and categorical variables, based on two categories ($\leq$ 48 hours and > 48 hours).

The following medical treatments were considered: misoprostol alone (treatment A), misoprostol supplemented with oxytocin (treatment B), and oxytocin alone (treatment C). Besides the mode of delivery and induction-delivery interval, the total dose of misoprostol (in μg), the number of misoprostol administrations, and complementation with postpartum curettage were also analyzed.

The maternal/obstetric characteristics selected were maternal age (< 20 years; 20 to 34 years; 35 and over); nulliparity (yes/no); gestational age (< 28/$\geq$ 28 weeks); previous caesarean section (yes/no); immature cervix (yes/no); and intact amniotic membranes (yes/no).

Statistical analysis was performed using the statistical package R. The continuous variables were expressed as mean and standard deviation (SD), and categorical variables were expressed as frequency and percentage.

This study follows the principles of the Declaration of Helsinki, and was approved by the research ethics committee of the teaching hospital under No. 21/2009.

Results

One hundred and seventy-one cases of IUFD gestations were analyzed. Misoprostol was administered in 29.2% of the cases. All administrations of misoprostol were performed by vaginal route, 32% of which were misoprostol alone (treatment A), and 68% of which were supplemented with intravenous oxytocin (treatment B). Oxytocin alone (treatment C) was given in 70.8% of cases. The means maternal age and gestational age were 26.1 years (SD = 7.6 years; range: 14 to 46 years) and 30.7 weeks (SD = 5.4 weeks; range: 18 to 42 weeks), respectively. One-third of the pregnancies were less than 28 weeks, and the mean birth weight was 1,707.2 g (SD = 967.1 g; range: 465 to 5,760 g). All mothers in the misoprostol groups (treatment A or treatment B), and 79.1% of those in the oxytocin group (treatment C) had intact amniotic membranes. Unfavorable cervix was the main maternal/obstetrical characteristic found in the treatment A group (100.0%) and treatment B group (97.1%) (Table 1).

The contribution for vaginal delivery of treatments A and B combined was as high as treatment C (98.0% vs. 96.7%). C-section occurred in one out of 34 mothers of the treatment B group, and in four out of 121 mothers of the treatment C group. The relation between the type of treatment and mode of delivery revealed that misoprostol alone and misoprostol supplemented by oxytocin had a similar effect to that of oxytocin alone (Table 2).

The majority (71%) of cases treated with misoprostol required a single administration of the medication (range: one to four administrations). Among the cases with a single administration, 75.0% and 69.7% were from group A and group B, respectively. Repeated administrations were performed

Table 1 – Maternal and obstetrical characteristics of 171 pregnancies with intrauterine fetal death, by type of labor induction or labor augmentation

Variable	Treatment A Misoprostol alone Yes (n = 16) n (%)	Treatment B Misoprostol plus oxytocin Yes (n = 34) n (%)	Treatment C Oxytocin alone Yes (n = 121) n (%)
Maternal age (years)			
13-19	6 (37.5)	11 (32.3)	26 (21.5)
20-34	10 (62.5)	16 (47.1)	75 (62.0)
$\geq$ 35	0 (0)	7 (20.6)	20 (16.5)
Nulliparity			
Yes	7 (43.7)	17 (50.0)	44 (36.4)
No	9 (56.3)	17 (50.0)	77 (63.6)
Prior cesarean section (n = 170)*			
Yes	3 (18.7)	6 (17.6)	18 (15.0)
No	13 (81.3)	28 (82.4)	102 (85.0)
Gestational age (n = 167)*			
$\leq$ 27 weeks	6 (37.5)	12 (35.3)	37 (31.6)
$\geq$ 28 weeks	10 (62.5)	22 (64.7)	80 (68.4)
Cervix status (n = 170)*			
Immature	16 (100.0)	33 (97.1)	57 (47.5)
Mature	0 (0)	1 (2.9)	63 (52.5)

* Results exclude women with incomplete data.

Table 2 – Mode of delivery of 171 pregnancies with intrauterine fetal death, by type of treatment for labor induction or labor augmentation

Type of treatment	Type of delivery		Total (n)
	Vaginal (n = 166) n (%)	Cesarean section (n = 5) n (%)	
Misoprostol in separate categories			
Treatment A (misoprostol alone)	16 (100.0)	0 (0)	16
Treatment B (misoprostol plus ocytocin)	33 (97.1)	1 (2.9)	34
Treatment C (Oxyciton)	117 (96.7)	4 (3.3)	121
Misoprostol in combined categories			
Treatment A and treatment B combined	49 (98.0)	1 (2.0)	50
Treatment C (Oxyciton)	117 (96.7)	4 (3.3)	121

twice (6.2% vs. 18.1%), three times (12.5% vs. 6.1%), and four times (6.2% vs. 6.1%) in group A and group B, respectively. Total value of dosage varied between 25 μg to 400 μg in the treatment A (mean: 98.4 μg; SD = 92.8) and treatment B groups (mean: 157.0 μg; SD = 92.7).

Forty percent of the women who received treatment with misoprostol underwent postpartum curettage. The procedure was less common in the treatment A group (31.2%) than in the treatment B group (44.1%). Overall, 62% of the patients with less than 28 weeks of gestational age underwent this surgical intervention.

The mean induction-delivery interval for the entire group was 15.37 hours (SD = 19.4 hours; range: 0.25 to 165 hours). Considering particular groups, the means were 20.15 hours (treatment A), 33.31 hours (treatment B) and 9.70 hours (treatment C) (Table 3).

At the end of 48 hours, 96% of the pregnancies were terminated, the majority of them (95.8%) by vaginal route. The proportions of cases treated with misoprostol alone, misoprostol plus oxytocin, and oxytocin alone who delivered vaginally within 48 hours were 100%, 96.7%, and 96.7%, respectively.

Discussion

Unlike findings based on RCTs conducted under ideal conditions, the present results reflect the role of misoprostol in obstetrics as practiced under the challenging conditions routinely faced in the public health services of the SUS. In these circumstances, misoprostol helped to resolve more unfavorable clinical cases presenting cervical immaturity and intact amniotic membrane, since the oxytocin group also included pregnant women in advanced stages of cervical dilation. The low number of induction failures and C-sections demonstrated the importance of misoprostol in the resolution of IUFD cases, in the second or third trimester, especially in low-income settings.

Comparing with other studies,[9–12] the present cases were resolved with a relatively lower mean total dose of misoprostol and a single administration. Other studies[13] report 400 μg to 600 μg of the preparation to have been effective in achieving uterine evacuation within 24 to 48 hours, and that lower doses prolonged the induction-delivery interval. Despite the prolonged induction-delivery interval observed in the present study, the lower number of administrations may have reduced the physical discomfort for a large number of these women, already distressed by the fetal death, since they had to endure only a single pelvic exam for the administration of vaginal misoprostol.

The present study included women with one (19/27), two (6/27), and three (2/27) prior C-sections (of any type), therefore having an increased risk for uterine rupture,[7] although this complication did not occur. Careful patient selection, individualization of doses administered, adequate monitoring of induction-delivery interval, and especially, the few cases with the combination of previous C-section and administration of misoprostol may have contributed to such results. According to Ramirez et al.,[14] 3.4% of the women who had uterine scarring and were submitted to medical labor induction for the assisted delivery of a dead fetus experienced uterine rupture in 19 American institutions. Although Ramirez et al.[14] have emphasized that uterine rupture did not show association with any drug employed, it is possible that it increases maternal morbidity/mortality in this scenario.

Overall, the frequency of previous C-section was greater than 15% considering all women, as well as in each treatment group analyzed *per se*. Generally, with fetal death, there

Table 3 – Mean induction-delivery interval of 171 pregnancies with intrauterine fetal death, by type of treatment for labor induction or labor augmentation.

Type of treatment	n (%)	Mean (hours)	SD	Minimum value	Maximum value
Treatment A (misoprostol alone)	16 (9.3)	20.15	15.8	4	60
Treatment B (misoprostol plus oxytocin)	34 (19.9)	33.31	29.6	6	165
Treatment C (oxytocin alone)	121 (70.8)	9.70	11.6	0.25	75

SD, standard deviation.

are reports in Brazil that a previous uterine scar reduces by 84% (OR 0.16; 95% CI: 0.04-0.71) the chance for drug-induced labor,[15] and increases by seven-fold (OR 7.0; 95% CI: 2.29-21.55) the chance for a repeat C-section as the route to deliver the dead fetus.[16] In the present study, none of the cases requiring a C-section was from the misoprostol alone group, as was also observed by Aquino et al.[10] However, one case with a previous C-section submitted to treatment B resulted in induction failure. In the treatment C cases, the C-section was conducted to guarantee the safety of the mother when the management of labor was affected by prior multiple cesarean deliveries (one case), systemic lupus erythematosus (one case), macrosomic fetus weighting 5,760 g (one case), and placental abruption associated with severe gestational hypertension (one case).

In the present study, postpartum curettage was much more frequent when compared with C-sections, but similar to other studies in proportion (40%).[17] It was used to check for placental residue retention, suspected by a clinical exam and/or imaging. Although postpartum curettage was not the objective of this study, it is important to highlight that early gestational age appears to influence the need for the procedure,[17] which was performed in over 60% of the patients with gestational age under 28 weeks.

As observed by others,[18–21] in the present study the vast majority of cases were delivered vaginally within 48 hours; however, the mean induction-delivery intervals were higher in the misoprostol groups than in the oxytocin group, as was found by Aquino et al.[10] It probably occurred because the oxytocin group had both women in situations which favored the labor induction and women whose labor had spontaneously started, and the labor was simply augmented by employing the drug, which partially explains the mean interval found.

Also, lack of achievement of fetal expulsion within 48 hours did not extend to C-section, and four out of the seven more prolonged cases were from the treatment B group; however, misoprostol was applied according to the protocol in only one of those four cases. According to Victora et al.,[22] in the standard clinical trial model, measures are taken for ensuring ideal compliance, including intensively trained staff, strictly controlled dosages, strong supervision, and monitoring of side effects. Such measures cannot be easily replicated under routine conditions. Despite the evidence, misoprostol was also initiated after oxytocin (three cases), creating a group of much worse prognosis (group B). The non-observance of the hospital protocols and the unavailability of the drug may have been reasons for such conduct. However, these questions are beyond the scope of the present study.

This study has limitations. Firstly, this was a retrospective descriptive study, with data collection dependent on the completeness of medical forms, making it impossible to analyze characteristics such as schooling and household income. This issue did not appear to affect the study results, since all participants were selected from a single public health service, possibly reflecting the socioeconomic status of women that attend SUS units in the region. Secondly, Bishop's score information was not available, so the option was made for using cervix description (mature or immature) instead. Although insufficient to replace the aforementioned index, this characteristic aided in the clinical classification of the cases at hand. Thirdly, it was not possible to classify some complaints occasionally reported on the medical charts as side effects of misoprostol, even though there are reports[9] that vomiting, nausea, fever, headache, and diarrhea are less common in the vaginal route than in the oral route. Finally, the major issue was the creation of the specific groups. Although uterus evacuation was the main goal in all groups, the cervix characteristics were different. Unfortunately, the oxytocin group was composed of women in advanced stages of cervical dilation, which made comparison among the groups difficult. The option was to show the results employing a descriptive design.

As advantages, this study was performed at a government-funded health service, which not only is a reference maternity-hospital for high-risk pregnancies, but also receives a wide variety of patients, and therefore better reflects the assistential reality of the SUS, as well as the profile of the assisted population. Taking into account the focus on dead fetus delivery, the size of the study population can be considered large.

Therefore, the induction of the delivery of dead fetuses was successful, reinforcing the utilization of misoprostol in government-provided healthcare services, and its ultimate incorporation in the treatment of cases in which oxytocin has not been successful. Nonetheless, its use must be carefully evaluated, guided by evidence-based protocols, and monitored by professionals capable of managing any occurrence associated with the induction. In relation to other Latin-American countries, the availability of misoprostol for vaginal administration in Brazil may be considered an advance. However, additional concerns might result from situations such as: (i) distribution restricted by law to hospitals,[4] (ii) expensive commercialization price, and (iii) product manufactured by only one local pharmaceutical company.[3] Such problems related to the supply chain of misoprostol may constitute obstacles for the renovation of the product's license, which may in the future result in the reduction of access to the medication already guaranteed for some indications in the field of reproductive health in Brazil.

Conclusion

In conclusion, misoprostol effectively contributed to the success of vaginal deliveries of dead fetuses, showing the importance of its application to resolve the cases presenting difficulty with the usual induction methods, and of its availability in public health services in Brazil.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database Syst Rev. 2010;14:CD004901.
2. Weeks A, Faúndes A. Misoprostol in obstetrics and gynecology. Int J Gynaecol Obstet. 2007;Suppl 2:S156–9.

3. Fernandez MM, Coeytaux F, de León RG, Harrison DL. Assessing the global availability of misoprostol. Int J Gynaecol Obstet. 2009;105:180–6.
4. Reis AMM, Perini E. Drug shortage: determinants, consequences and management. Ciênc Saúde Coletiva [online]. 2008;13 suppl:603–10.
5. Clark S, Blum J, Blanchard K, Galvão L, Fletcher H, Winikoff B. Misoprostol use in obstetrics and gynecology in Brazil, Jamaica, and the United States. Int J Gynaecol Obstet. 2002;76:65–74.
6. Elati A, Weeks AD. The use of misoprostol in obstetrics and gynecology. BJOG. 2009;116 Suppl 1:61–9.
7. Faúndes A (Ed). Misoprostol use in obstetrics and gynecology. Federación Latinoamericana de Sociedades de Obstetrícia y Ginecología (FLASOG); 2007.
8. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Labor induction (chapter 22). In: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, editors. Williams Obstetrics. 23rd ed. New York: McGraw-Hill; 2010.
9. Nyende L, Towobola OA, Mabina MH. Comparison of vaginal and oral misoprostol, for the induction of labour in women with intra-uterine fetal death. East Afr Med J. 2004;81:179–82.
10. Aquino MMA, Guedes AC, Mesquita MRS, Hernandez M, Cecatti JG. Obstetrical management of fetal death. Rev Bras Ginecol Obstet. 1998;20:145–9.
11. Mariani Neto C, Leão EJ, Barreto EM, Kenj G, De Aquino MM, Tuffi VH. Use of misoprostol for labor induction in stillbirth. Rev Paul Med. 1987;105:325–8.
12. El-Gharib MN, Elebyary MT. Low-dose vaginal misoprostol in the management of intrauterine fetal death. J Matern Fetal Neonatal Med. 2011;24:1239–42.
13. Gómez Ponce de León R, Wing DA. Misoprostol for termination of pregnancy with intrauterine fetal demise in the second and third trimester of pregnancy – a systematic review. Contraception. 2009;79:259–71.
14. Ramirez MM, Gilbert S, Landon MB, Rouse DJ, Spong CY, Varner MW, et al. Mode of delivery in women with antepartum fetal death and prior cesarean delivery. Am J Perinatol. 2010;27:825–30.
15. Sampaio AG, Souza ASR, Noronha Neto C. Factors associated with induced delivery in pregnant women with a dead fetus after the 20th week of gestation. Rev Bras Saúde Matern Infant. 2011;11:125–31.
16. Sampaio AG, Souza ASR. Cesarean section in fetal death. Rev Bras Ginecol Obstet. 2010;32:169–75.
17. Van Mensel K, Claerhout F, Debois P, Keirse MJ, Hanssens M. A randomized controlled trial of misoprostol and sulprostone to end pregnancy after fetal death. Obstet Gynecol Int. 2009;2009:496320.
18. Fawole AO, Adekunle AO, Sotiloye OS, Arowojolu AO, Otolorin EO. Experience with intravaginal misoprostol in the management of intra-uterine fetal death. Afr J Med Med Sci. 2004;33:105–8.
19. Nakintu N. A comparative study of vaginal misoprostol and intravenous oxytocin for induction of labour in women with intra uterine fetal death in Mulago Hospital. Uganda Afr Health Sci. 2001;1:55–9.
20. Chittacharoen A, Herabutya Y, Punyavachira P. A randomized trial of oral and vaginal misoprostol to manage delivery in cases of fetal death. Obstet Gynecol. 2003;101:70–3.
21. Bugalho A, Bique C, Machungo F, Faúndes A. Induction of labor with intravaginal misoprostol in intrauterine fetal death. Am J Obstet Gynecol. 1994;171:538–41.
22. Victora CG, Habicht JP, Bryce J. Evidence-based public health: moving beyond randomized trials. Am J Public Health. 2004;94:400–5.