THE USE OF HERBAL MEDICINES DURING PREGNANCY AND PERINATAL MORTALITY IN TUMPAT DISTRICT, KELANTAN, MALAYSIA

Azriani Ab Rahman[1], Zulkifli Ahmad[1], Lin Naing[2], Siti Amrah Sulaiman[3], Abdul Manaf Hamid[1] and Wan Nudri Wan Daud[1]

[1]Department of Community Medicine, [2]School of Dental Sciences, [3]Departments of Pharmacology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Krian, Kelantan, Malaysia

Abstract. The objective of this case-control study was to determine the association between herbal medicine use during pregnancy and perinatal mortality in Tumpat District, Kelantan, Malaysia. Cases were mothers who gave birth from June 2002 to June 2005 with a history of perinatal mortality, while controls were those without a history of perinatal infant mortality. A total of 316 mothers (106 cases and 210 controls) were interviewed. The use of unidentified herbs prepared by traditional midwives and other types of herbal medicines during the first trimester of pregnancy were positively associated with perinatal mortality (OR=5.24, 95% CI=1.13; 24.23 and OR=8.90, 95%, CI=1.35; 58.53, respectively). The use of unidentified "Orang Asli" herbs and coconut oil during the third trimester of pregnancy were negatively associated with perinatal mortality in Tumpat (OR=0.10, 95% CI=0.02; 0.59 and OR=0.48, 95% CI=0.25; 0.92, respectively). These findings suggest the use of unidentified "Orang Asli" herbs and coconut oil in late pregnancy are protective against perinatal mortality, while the use of unidentified herbs prepared by traditional midwives and other types of herbal medicines in early pregnancy has an increased risk of perinatal infant mortality. Pharmacological studies to confirm and identify the compounds in these herbs and their effects on the fetus should be conducted in the future.

INTRODUCTION

Herbal medicines are defined as plant-derived material or preparations with therapeutic benefits, and contain raw or processed ingredients from one or more plants (WHO, 2000). The use of herbal medicines during pregnancy is common, ranging from 7.0 to 55.0% (Tiran, 2003). Perinatal mortality is defined as death of a fetus weighing at least 500 g or born after 22 weeks gestation or a crown rump heel length equal to or greater than 25 cm, or early neonatal death (0-6 days) (MOH, 2000). In 2000, the perinatal mortality rate was 47 per 1,000 births in the world (WHO, 2006). In the study area, Tumpat, the perinatal mortality rate in 2003 was 13.68 per 1,000 births (Kelantan State Health Department, 2004) which was higher than the rate in Kelantan (11.59 per 1,000 births) (Kelantan State Health Department, 2004) and in Malaysia overall (9.1 per 1,000 births) (MOH, 2004). Several factors, such as low maternal educational level, low household income, too young and too old mothers, primiparity, grandmultiparity and maternal diseases have been among the factors found to be associated with perinatal death (Kliegman. 1998). Al-

Correspondence: Dr Azriani Ab Rahman, Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Krian, Kelantan, Malaysia.
Fax: 609-765 3370
E-mail : azriani@kb.usm.my

though there are no published studies directly linking herbal medicine use in pregnancy with perinatal death, several studies have found herbal medicine use in pregnancy is associated with congenital malformations (Takei *et al*, 1997; Chan *et al*, 2003; Noordalilati *et al*, 2004), intrauterine growth retardation, decreased fetal survival rates (Sulaiman *et al*, 2001), low birth weight (Morris and Mdlalose, 1991), fetal distress (Mabina *et al*, 1997), fetal hypoxia and premature delivery as a results of uterine hyperstimulation (Veale *et al*, 1998), which may lead to perinatal mortality.

The objective of this study was to determine the association between herbal medicine use in pregnancy and perinatal mortality in Tumpat District, Kelantan, Malaysia.

MATERIALS AND METHODS

Tumpat District is one of ten districts in Kelantan. It is a costal area, about 21 km from Kota Bharu, the capital of Kelantan and about 1 km from the Thai border. Most of the people there are farmers or fishermen. The majority are Malays.

A case-control study was carried out in 2005. The inclusion criteria for cases were women who gave birth from June 2002 to June 2005, who were recorded in the birth registration records of Tumpat District and had a history of perinatal mortality. The inclusion criteria for controls were those with no history of perinatal mortality, giving birth during the same period of time. All cases who fulfilled the inclusion criteria were included. A simple random sampling method was used to select controls. A sample size calculation was done using PS Software, version 1.0.13 (Dupont and Plummer, 1997). Taking a significance level of 0.05, a study power of 80%, a detectable odds ratio of 2.0 (women with a history of perinatal mortality were 2.0 times more likely to use herbal medicines during pregnancy compared to those without perinatal mortal-

ity), a proportion of herbal medicine exposure among controls of 0.46 (estimated by the proportion of herbal medicine use during pregnancy among women attending antenatal clinics, Hospital Universiti Sains Malaysia) and a ratio of cases to controls of 2, the minimum sample size required was 300 subjects, 100 cases and 200 controls.

The patients were interviewed using a structured questionnaire by the first author. The interviewer gave a definition of herbal medicines to the mothers. In this study, mothers were considered herbal medicines users if they took herbal medicines orally in any form, such as solutions, capsules, tablets or in raw form, at any amount during any trimester of pregnancy. Preparations consumed as nutriments or as food additives were not considered as herbal medicines. The patients were also asked whether they had taken herbal medicines before they conceived. For those who took herbal medicines before becoming pregnant, they were asked to recall the last time they took the medicines to determine whether they were taken during pregnancy. To help mothers to recall, a list of commonly used herbal medicines was shown to the subjects as examples. A list of common indications for using herbal medicines was also shown and the subjects who were asked whether any herbal medicines had been used. Local traditional midwives, homeopathy practitioners and pharmacists were interviewed in an effort to confirm whether the products were herbal medicine products and to identify the specific herbal contents of the products.

Sociodemographic and maternal disease variables of the cases and controls were tabulated for descriptive statistics. Binary logistic regression was used to determine the association between the use of herbal medicines during pregnancy and perinatal mortality adjusting for the known risk factors. Despite many factors that are known to be associated with perinatal mortality, only some of the

factors were included in our study. The selected factors were those in which accurate information could be obtained from available research tools or textbooks. The selected factors were parity, maternal disease, age, total household monthly income, race, education, husband smoking status, patient smoking status, multiple pregnancy, HIV and syphilis infection. The preliminary main effects model was fit by the independent variables, including herbal medicine use, as research question variables and all known risk factors adjusting for variables. Model fitness was checked by the Hosmer-Lemeshow goodness-of-fit test and ROC curve. Influential cases were identified by influential statistics, namely delta beta, delta chi square and delta deviance. A case was considered an influential outlier if delta beta ≥ 1, delta chi-square and delta deviance ≥ 4 (Hosmer, 2000). Results were analyzed using Stata version 8.

This study was approved by the Research and Ethics Committee, Universiti Sains Malaysia (USM) and Ministry of Health, Malaysia.

RESULTS

All 316 mothers (106 cases and 210 controls) consented to be interviewed. Table 1 showed the sociodemographic and maternal characteristics for cases and controls. Cases were older and had greater parity. A higher proportion of cases had maternal disease and multiple pregnancies. The cases had lower educational level. A lower proportion of mothers who were housewives was observed among cases. The total monthly household income was lower among cases. There were no significant differences in race, marital status or spouse smoking between cases and controls. All the mothers were non-smokers. HIV and VDRL were negative for all mothers.

There were 41 cases (38.7%) and 108 controls (51.4%) who used at least one type of herbal medicine during pregnancy in this study. The most common herbal medicine used by cases (46.3%) and controls (63.9%) in this study was coconut oil, which was ingested during the third trimester of pregnancy only. The most common indication for using herbal medicines during pregnancy among cases (61.0%) and controls (89.8%) was to facilitate labor.

Simple logistic regression (Table 2) revealed significant herbal variables were the use of unidentified "Orang Asli" herbs and coconut oil during the third trimester of pregnancy and the use of unidentified herbs prepared by traditional midwives during the first trimester of pregnancy.

On multiple logistic regression (Table 3), the significant herbal variables after adjusting for parity, maternal disease, age, income, race, education and husband smoking status were the use of unidentified "Orang Asli" herbs and coconut oil during the third trimester of pregnancy, the use of unidentified herbs prepared by traditional midwives and other types of herbal medicines during the first trimester of pregnancy. The use of unidentified "Orang Asli" herbs and coconut oil during the third trimester of pregnancy was protective for perinatal mortality. The odds of perinatal mortality for mothers who took the unidentified "Orang Asli" herbs was 90.0% less (OR = 0.10). The odds of perinatal mortality for those who took coconut oil was 52.0% less than those who did not take it (OR= 0.48). The use of unidentified herbs prepared by traditional midwives and other types of herbal medicines during the first trimester of pregnancy were positively associated with perinatal mortality. Those who used unidentified herbs prepared by traditional midwives during the first trimester of pregnancy were 5.24 times more likely of having perinatal mortality. Those who used other types of herbal medicines during the first trimester of pregnancy were 8.90 times more likely of having perinatal mortality.

Table 1
Sociodemographic and maternal characteristics in cases and controls.

Variables	Cases n= 106	Controls n = 210	Test statistic (df)[a]	p-value
Age (years)	33.5 (7.77)[b]	30.5 (6.54)[b]	-3.42[d] (182)	0.001[d]
25-34	34 (32.1)[c]	111 (52.9)[c]	17.98[e] (2)	<0.001[e]
17-24	19 (17.9)[c]	43 (20.5)[c]		
≥ 35	53 (50.0)[c]	56 (26.7)[c]		
Income (RM)	678.30 (511[b])	840.43 (678)[b]	2.36[d] (271)	0.019[d]
<500	41 (38.7)[c]	62 (29.5)[c]	3.36[e] (2)	0.186[e]
500-1,300	53 (50.0)[c]	113 (53.6)[c]		
>1,300	12 (11.3)[c]	35 (16.7)[c]		
Parity	4.9 (3.49)[b]	3.6 (2.29)[b]	-3.60[d] (152)	<0.001[d]
2-5	42 (39.6)[c]	130 (61.9)[c]	20.30[e] (2)	<0.001[e]
Race group				0.232[f]
Malay	104 (98.1)[c]	204 (97.1)[c]		
Non Malay	2 (1.9)[c]	6 (2.9)[c]		
Marital status				0.112[f]
Married	104 (98.1)[c]	210 (100.0)[c]		
Single (unmarried)	2 (1.9)[c]	0 (0.0)[c]		
Husband's smoking status	66 (62.3)[c]	121 (57.6)[c]	0.63[e] (1)	0.428[e]
Multiple pregnancy	5 (4.7)[c]	0 (0.0)[c]		0.004[f]
1	21 (19.8)[c]	42 (20.0)[c]		
≥ 6	43 (40.6)[c]	38 (18.1)[c]		
Education			7.99[e] (2)	<0.001[e]
No formal education	10 (9.4)[c]	1 (0.5)[c]		
Primary	46 (43.4)[c]	78 (37.1)[c]		
Secondary	47 (44.3)[c]	115 (54.8)[c]		
University / college	3 (2.8)[c]	16 (7.6)[c]		
Occupation			7.26[e] (1)	0.007[e]
Housewife	83 (78.3)[c]	188 (89.5)[c]		
Employed	23 (21.7)[c]	22 (10.5)[c]		
Maternal diseases [g]	30 (28.3)[c]	25 (11.9)[c]	13.17[e] (1)	<0.001[e]

[a]Degree of freedom, [b] mean (SD), [c] n (%), [d] t-statistic, independent t-test, [e] Pearson chi-square, [f] Fisher's exact test, [g] maternal diseases include diabetes mellitus (n=18), hypertensive disorder in pregnancy (n=29), thyrotoxicosis (n=5), HbH disease (n=1)

DISCUSSION

There are no published studies on the use of herbal medicines during pregnancy and their association with perinatal mortality. This study found the use of unidentified "Orang Asli" herbs and coconut oil during the third trimester of pregnancy were protective factors against peri-natal mortality. It is difficult to explain the protective effect found. The traditional indication for taking these herbs is to facilitate delivery as mothers believe that unidentified "Orang Asli" herbs stimulate cervical opening, thus promoting faster delivery. Mothers also believe that coconut oil may result in smooth passage of the baby through the birth canal, preventing

Table 2
Use of herbal medicines during pregnancy and perinatal mortality analysed by simple binary logistic regression.

Variables (use of specific types of herbal medicines in specific trimester of pregnancy)	Case (n=106) n (%)	Control (n = 210) n (%)	Crude OR [a]	95% CI OR [b]	p-value of LR Stat[c]
Unidentified 'Orang Asli' herbs in 3rd trimester	2 (1.9)	21 (10.0)	0.17	0.04, .75	0.004
Coconut oil in 3rd trimester	19 (17.9)	69 (32.9)	0.45	0.25, .79	0.004
Unidentified herbs prepared by traditional midwives in 1st trimester	7 (6.6)	4 (1.9)	3.64	1.04, 12.73	0.038
Unidentified herbs prepared by traditional midwives in 2nd or 3rd trimester	1 (0.9)	8 (3.8)	0.24	0.03, 1.95	0.114
Other types of herbal medicines in 1st trimester[d]	8 (7.5)	8 (3.8)	2.06	0.75, 5.66	0.164
Other types of herbal medicines in 2nd trimester[e]	3 (2.8)	7 (3.3)	0.84	0.21, 3.33	0.808
Other types of herbal medicines in 3rd trimester[f]	6 (5.7)	8 (3.8)	1.52	0.51, 4.48	0.459
"Sanggul Kacip Fatimah" in 3rd trimester	3 (2.8)	6 (2.9)	0.99	0.24, 4.04	0.989
Other types of "Kacip Fatimah" (Labisia patoina, pumila) in 1st trimester	6 (5.7)	7 (3.3)	1.74	0.57, 5.31	0.337
"Ketam Uri" use in 2nd or 3rd trimester	3 (2.8)	2 (1.0)	3.03	0.50, 18.41	0.223
"Manjakani" (Croton caudatus) use in 1st trimester	1 (0.9)	3 (1.4)	0.65	0.07, 6.39	0.709

[a] Crude odds ratio; [b]Confidence interval of odds ratio; [c]Likelihood ratio statistic; [d]other types of herbal medicines used during 1st trimester of pregnancy include "celaka" (Plumbago zeylonica) root (n=3), "gelam" (Melacieuca cajupati) leaf (n=1), "tongkat ali" (Eurycoma longifolia jack) juice (n=1), "sirih" (Piper bettle) leaf (n=1), "stunjang bumi" (Prismatomeris tetranda) root ((n=1), "mas secotek" (Ficus deltoides) (n=1), "mata kucing Keling" fruit (n=1), pineapple fruit (n=1), "Mengkudu" (Morinda elliptica) juice (n=1), "ganoderma" (n=1), "tongkui" root (n=1), boiled juice of "durian" skin (n=1), coconut juice (n=2), "kembang semangkuk" (Scaphium macropodum) flower (n=1), sea weed (n=1), gingko (Gingko biloba) fruit (n=1), "tamar" fruit (n=1); [e]other types of herbal medicines used during 2nd trimester of pregnancy, include "ganoderma" (n=3), sea weed (n=1), "tamar" fruit (n=2), gingko (Gingko biloba) fruit (n=1), "tongkat ali" (Eurycoma longifolia jack) (n=1), "mengkudu" (Morinda elliptica) juice (n=1), "mata kucing keling" fruit (n=1); [f]other types of herbal medicines used during 3rd trimester of pregnancy, include coconut juice (n=2), "ganoderma" (n=2), sea weed (n=1), "tamar" fruit (n=2), boiled juice of "durian" skin (n=2), "tongkat ali" (Eurycoma longifolia jack) (n=1), "kembang semangkuk" (Scaphium macropodum) flower (n=1), "mengkudu" (Morinda elliptica) juice (n=1), "mata kucing keling" fruit (n=1), gingko (Gingko biloba) fruit (n=1)

complications, such as post-term pregnancy and prolonged labor, which are known to be contributing factors to fetal death. There may be benefits of these herbs in facilitating labor and reducing intrapartum complications, which are not currently known. However, this interesting finding should be confirmed by pharmacological study to identify the compounds in these herbs and to evaluate the effects of these compounds on the fetus.

Table 3
Use of herbal medicines during pregnancy and perinatal mortality analysed by multiple binary logistic regression[a]

Variables (use of specific types of herbal medicines in specific trimester of pregnancy)	Adj OR[b]	95%CI OR[c]	p-value of LR Stat[d]
Unidentified 'Orang Asli' herbs in 3rd trimester			
No	1.00		0.001
Yes	0.10	0.02, 0.59	
Coconut oil in 3rd trimester			
No	1.00		0.024
Yes	0.48	0.25, 0.92	
Unidentified herbs prepared by traditional midwives in 1st trimester			
No	1.00		0.029
Yes	5.24	1.13, 24.23	
Other types of herbal medicines in 1st trimester [e]			
No	1.00		0.017
Yes	8.90	1.35, 58.53	
Unidentified herbs prepared by traditional midwives in 2nd or 3rd trimester			
No	1.00		0.160
Yes	0.24	0.02, 2.40	
Other types of herbal medicines in 2nd trimester[f]			
No	1.00		0.056
Yes	0.03	0.00, 1.11	
Other types of herbal medicines in 3rd trimester[g]			
No	1.00		0.311
Yes	3.56	0.28, 45.41	
"Sanggul Kacip Fatimah" in 3rd trimester			
No	1.00		0.817
Yes	1.21	0.25, 5.87	
Other types of "Kacip Fatimah" (*Labisia pumila, patoina*) in 1st trimester			
No	1.00		0.306
Yes	1.97	0.54, 7.25	
Other types of herbal medicines in 3rd trimester[g]			
No	1.00		0.311
Yes	3.56	0.28, 45.41	
"Ketam Uri" in 2nd or 3rd trimester			
No	1.00		0.101
Yes	7.74	0.64, 93.32	
"Manjakani" (*Croton caudatus*) in 1st trimester			
No	1.00		0.855
Yes	0.80	0.07, 9.25	

[a]adjusted for parity, maternal diseases, age, income, race, education, spouse smoking status; [b]Adjusted odds ratio; [c]Confidence interval of adjusted odds ratio; [d]Likelihood ratio statistic Hosmer-Lemeshow goodness-of-fit statistics chi-square p-value = 0.557. ROC curve =0.803.No influential outliers identified.

This study measured perinatal mortality as a birth outcome, while other studies focused on perinatal morbidity, which can lead to perinatal mortality. Several studies found that herbal medicines taken to facilitate labor caused adverse fetal effects. In South Africa, fetal distress was related to the consumption of local herbal medicines taken to facilitate

labor. About 55.6% of mothers using herbal medicines had meconium staining of amniotic fluid, an indication of fetal distress (Mabina *et al*, 1997). In another study, Glover *et al* (2003) reported uterine hyperstimulation occurred at 39 weeks of gestation when a mother took black cohosh to "induce labor". The infant suffered from fetal distress and thick meconium aspiration. Traditional herbal medicines can lead to strong, continuous uterine contractions not corresponding to the slow dilatation of the cervix. As a result, they may cause acidosis in the mother, followed by fetal distress (Rolanda and Sally, 2006). Meconium-stained amniotic fluid is associated with perinatal asphyxia and meconium aspiration syndrome (MAS). Meconium aspiration is one of the most common causes of perinatal mortality (Kliegman, 1998). Laboratory studies found that *Isihlambezo*, a traditional herbal medicine used to stimulate the tonicity and frequency of uterine contractions, augments the effects of oxytocin on isolated rat uterus. Used inappropriately, it may lead to premature labor (Varga and Veale, 1997), which is another common cause of perinatal mortality (Kliegman, 1998). In our study, many mothers ingested unidentified "Orang Asli" herbs and coconut oil at term, before the onset of labor. As these herbal medicines are generally taken only at term, the possibility of premature delivery is avoided. However, our study was not able to rule out the possibility of uterine hyperstimulation induced by these herbs. The mothers took only one tablet of unidentified "Orang Asli" herbs, while they took only one teaspoon or table spoon of coconut oil. The practice of consuming herbal medicines in relatively small doses at term is unlikely to cause adverse effects on the fetus. The health impact of herbal medicines is highly dependent on amount, concentration and stage of pregnancy (Varga and Veale, 1997).

We found the use of unidentified herbs prepared by traditional midwives and other types of herbal medicines during the first trimester of pregnancy were risk factors for perinatal mortality. These herbs may contain chemical compounds which may be teratogenic. Exposure of the embryo to teratogens during the first trimester of pregnancy may cause congenital anomalies because fetal tissues and organ systems are developing rapidly during this period (Moore, 1998). A local herb, *Andrographis paniculata* (Hempedu bumi) given orally to rats during early pregnancy caused teratogenic effects leading to major congenital malformations (Noordalilati *et al*, 2004). Congenital malformations are a common cause of perinatal mortality (Kliegman, 1998). In Kelantan, congenital malformations cause 17.7% of perinatal mortality in 2001 (Kelantan State Health Department, 2001).

This study suggests some herbs are harmful, while others may be protective for the fetus. These findings should be confirmed by conducting further studies to identify pharmacological compounds of these herbs and evaluate the effects of these compounds on the fetus.

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