Risk of Fetal Abnormalities after Intake of Herbal Medicinal Products and Western Pharmaceutical Products in Pregnancy

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Objectives:
To identify the risk of fetal abnormalities after intake of herbal medicinal products (HMPs) in pregnancy.

Methods:
A retrospective review of our database (from January 1995 to December 2001) and a prospective study (from January 2002 to June 2006) were conducted in a teaching hospital to identify the pattern of HMP and western pharmaceutical product (WPP) usage and corresponding fetal outcomes. All women with a history of intake of HMP and / or WPP were referred to our prenatal diagnostic clinic for assessment and counselling. Paediatricians assessed all babies after delivery.

Results:
Of 1351 women studied, 206 had taken HMPs and 1145 had taken WPPs during their index pregnancies. More women were nulliparous among those who had taken WPPs than those who had taken HMPs (63% vs 55%) [p=0.04]. There were no significant differences in the marital status, family incomes, and educational levels between the HMP and WPP groups. The number of drugs taken in the WPP (2.5) group was significantly greater than that in the HMP (1.5) group. Common reasons for intake of HMPs were flu-like symptoms, to promote health, for menstrual problems, gastrointestinal problems, and pain relief. Seven women took HMPs and 99 took WPPs for weight reduction. The number of sonographic fetal abnormalities in the HMP and WPP groups were 3 (1.5%) and 22 (1.9%), respectively. This difference was not significant. Also there were no significant differences between the two groups in the rates of silent miscarriage, and termination of pregnancy for anxiety. One woman in the HMP group and 14 women in the WPP group requested termination of pregnancy.

Conclusion:
After the intake of the HMPs or WPPs taken by our patient cohort, the risk of fetal abnormalities was not higher than that of the general unexposed population. There was also no demonstrable increase in the risk of fetal growth restriction or silent miscarriage in either group.
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Introduction

Many pregnant women take medications and the proportion doing so may be as high as 99%, according to a survey in France[1]. It has also been reported that more than 10% of pregnant women in the western world use

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Table 1. Demographic data of pregnant women taking herbal medicinal products (HMPs) or western pharmaceutical products (WPPs)

Demographic data	HMP (n=206)	WPP (n=1145)	p Value
Mean (standard deviation) age (years)	31.6 (4.7)	30.9 (5.0)	0.034
Nulliparous	114 (55%)	720 (63%)	0.040
Mean No. of drugs taken	1.5	2.5	<0.001

herbal medicinal products (HMPs)[2-6]. Most of them use HMPs as dietary supplements rather than to treat medical disorders. Recently, Chuang et al[7] reported a high user rate of HMP (24%) in Taiwan Chinese. Reasons for intake of HMPs included: flu, cold, gastrointestinal upset, abdominal pain, musculoskeletal pain, as vitamin supplements, to combat threatened miscarriage and infection[8-11].

Despite the general belief that HMPs promote health, evidence is scarce. The commonest quoted reason for their use in the general population was to avoid side-effects of western pharmaceutical products (WPPs)[12]. Although the public, in general, believes that HMPs are without risk to their health[13], a review came to the conclusion that there are risks associated with HMPs[3].

In 2002, Leung et al[14] reported the use of HMPs by pregnant women in Hong Kong, and concluded that the risk of teratogenicity was not significantly higher than that for WPP users. However, their study was retrospective and small. The present study was a continuation of the investigation[14] and included prospective data. Its objective was to compare the fetal outcomes in HMP and WPP users.

Methods

This study entailed a retrospective review of our database (from January 1995 to December 2001) and a prospective evaluation (from January 2002 to June 2006). All the retrospective data had been presented in a previous paper[14]. The entire study was conducted in a teaching hospital, where the pattern of HMP and WPP usage and fetal outcomes were identified. Our centre accepted referrals from private doctors as well as other hospitals for prenatal diagnosis.

During the first antenatal visit, all women who had taken any HMP or WPP 1 month before or during their index pregnancy were identified via direct questioning by midwives. All such users were referred to our prenatal diagnostic clinic for assessment and counselling. The names, dosages, and the perceived indications for these medications were recorded. Literature search on drug teratogenicity was performed and counselling was provided accordingly. Prenatal diagnostic methods included two-dimensional morphology scan and, in the later part of our study, three-dimensional ultrasound examination. Since the teratogenic effects of HMPs are largely unknown, patients were counselled to that effect. In the WPP group, the women were counselled according to the results of our literature search. All medical records were traced and reviewed, and the main fetal outcome measures recorded included: congenital abnormalities, miscarriages, and terminations of pregnancy. Paediatricians assessed all babies after delivery. The outcomes of the HMP and WPP groups were compared. If a woman had taken both HMP and WPP, she was assigned into the category which she herself worried about most. The prevalence of fetal congenital malformations in the general population was obtained from the data generated from a previous paper from our department covering a similar study period[15].

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US). Student's *t* test was used to evaluate continuous data and the Chi-square test for discrete data.

Results

From January 1995 to June 2006, a total of 1351 pregnant women were identified, of which 206 had taken HMPs and 1145 had taken WPPs 1 month before and / or during their index pregnancies.

More women in the WPP group were nulliparous: 720 (63%) compared to 114 (55%) in the HMP group (Table 1), this difference being significant (p=0.040).

Table 2. Level of education, marital status, and family incomes of pregnant women taking herbal medicinal products (HMPs) or western pharmaceutical products (WPPs)

	HMP (n=206)	WPP (n=1145)	Subtotal	p Value
Education				0.123
Primary	16 (8%)	52 (5%)	68	
Secondary	138 (67%)	758 (66%)	896	
Tertiary	49 (24%)	307 (27%)	356	
Missing data	3	28	31	
Total	**206**	**1145**	**1351**	
Marital status				0.07
Married	203 (99%)	1099 (96%)	1302	
Single	3 (1%)	46 (4%)	49	
Total	**206**	**1145**	**1351**	
Mean (standard deviation) family income (HK$/month)	22,587 (22,661)	32,656 (51,110)		0.465
Missing data	174	860		
Total	**206**	**1145**	**1351**	

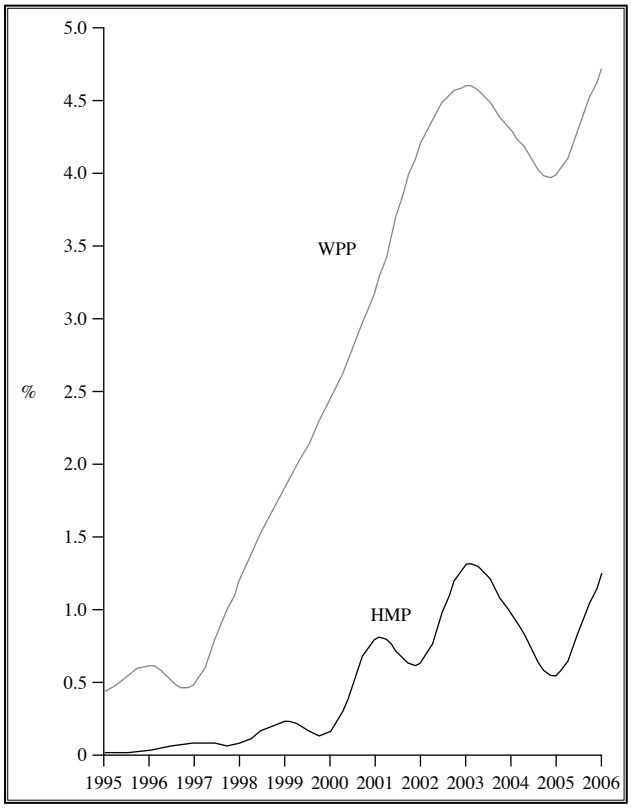

Figure. Proportions of herbal medicinal product (HMP) and western pharmaceutical product (WPP) users (per total number of deliveries) from January 1995 to first half of 2006

The average number of drugs taken per woman in the WPP group (2.5) was significantly greater than in those taking HMPs (1.5) [p<0.001]. There were no differences in the marital status, family income, and educational level of women in the two groups (Table 2).

The proportion of pregnant women taking HMPs increased from 0.01% in 1995 to 1.32% in 2003, and then fluctuated around that level (Figure). A similar pattern was observed for WPP users. The corresponding figures for WPP consumers were 0.44% in 1995 and 4.60% in 2003.

The reported reasons for taking HMPs or WPPs differed significantly (p<0.001). The common reasons for intake of HMPs were flu-like symptoms (30%), promotion of health (20%), menstrual problems (12%), gastrointestinal problems (11%), and pain relief (9%) [Table 3]. The main reasons for intake of WPPs were medical problems (38%), flu-like symptoms (25%), infection (9%), and weight reduction (9%). Though it is generally not advisable to undertake weight reduction in pregnancy, seven women took HMPs and 99 took WPPs for this purpose.

There were no statistical differences in the proportions of sonographic abnormalities, silent miscarriages, and terminations of pregnancy for maternal anxiety between the HMP and WPP groups (Tables 4 and 5). The number of sonographic fetal abnormalities in the former were three (1.5%) and in the latter 22 (1.9%).

Table 3. Indications for taking herbal medicinal products (HMPs) and western pharmaceutical products (WPPs) in pregnancy*

Indication	No. (%)	
	HMP (n=206)	WPP (n=1145)
Flu-like symptoms	61 (30)	287 (25)
Promotion of health	42 (20)	40 (3)
Menstrual problem	25 (12)	0
Gastrointestinal problem	22 (11)	0
Pain relief	18 (9)	7 (1)
Weight reduction	7 (3)	99 (9)
Skin	6 (3)	0
Threatened miscarriage	5 (2)	0
Medical problems	4 (2)	435 (38)
Pregnancy complication	4 (2)	0
Termination of pregnancy	3 (1)	24 (2)
Infection	2 (1)	100 (9)
Subfertility	1 (0.5)	0
Vaccination	0	37 (3)
Others	1 (0.5)	0
Unknown	5 (2)	9 (1)
Soft drugs	0	42 (4)
Oral contraceptive pills	0	65 (6)

* $p<0.001$, Chi-square test

Table 4. Fetal outcome for pregnant women taking herbal medicinal products (HMPs) and western pharmaceutical products (WPPs)

Fetal outcome	HMP (n=206)	WPP (n=1145)	p Value
Sonographic abnormalities	3 (1.5%)	22 (1.9%)	0.70
Silent miscarriage	5 (2.4%)	21 (1.8%)	0.66
Termination of pregnancy	1 (0.5%)	14 (1.2%)	0.80
Normal	197 (95.6%)	1088 (95.0%)	-
Mean (standard deviation) birth weight (g)	3046 (807)	2978 (803)	0.36
Total	**206**	**1145**	**-**

Newborn birth weights in the two groups were similar.

Discussion

In our 2002 retrospective study[14], we reported that the 3.3% point prevalence of fetal anomalies in pregnant women who took HMPs was not significantly higher than that in the pregnant women who took WPPs (0.8%). In the present study that included prospective data, we confirmed that there was no significant difference in the risk of congenital abnormalities between the two user groups (1.5% vs 1.9%).

Ethnic variations and cultural beliefs are important in influencing human behaviour. Dietary supplementation was the commonest reason for intake of HMP in Finland[2], whereas in Hong Kong flu-like symptoms and promotion of health were the common reasons.

There was an increase in the proportion of HMP

Table 5. Fetal anomalies detected after intake of herbal medicinal products (HMPs) and western pharmaceutical products (WPPs)

Fetal anomalies	HMP	WPP
Hypoplastic right heart syndrome	1	
Body stalk anomaly	1	
Multiple fetal anomaly	1	
Prominent renal pelvis		5
Cleft lip and palate		3
Ventricular septal defect		1
Absent right hand		1
Trisomy 21		1
Encephalocele		1
Exencephaly		1
Pyelo-ureteric junction obstruction		1
Intrauterine growth restriction		1
Hydrocephaly + club foot		1
Gastroschisis		1
Ascites		1
Echogenic bowel		1
Congenital heart block		1
47XY + marker chromosomes		1
Mitochrondrial defect		1
Total	**3**	**22**

and WPP users from 1995 to 2003. This could be due to a genuine increase in the use of medications. Another possibility was that more users of WPPs and HMPs were identified in the antenatal clinic over the years by virtue of explicit questioning by our midwives. After 2003, there was no further increase in the use of these medications. We postulate that in 2003 more women became aware of the side-effects of HMPs or WPPs due to the publicity aroused by various publications related to possible adverse effects of medications on pregnancy.

In 2002, Ernst[3] produced a review in which HMPs were associated with potential risks to pregnant women and fetuses. The potential benefits of HMPs for pregnant women were difficult to assess and very few trials on this topic have been published. The only reasonably well-researched HMP is ginger, which was shown to be an effective treatment for nausea and vomiting, according to a recent systematic review[3]. Owing to such a degree of uncertainty, firm conclusions were difficult to adopt. The author therefore preferred to consider all HMPs to be contraindicated during pregnancy[3].

Our study suggests that there seems to be no additional fetal risk due to the HMPs and WPPs taken by our cohort. After intake of either, the risk of fetal anomaly was around 2% which is similar to fetal anomaly rate in low-risk groups[15]. We believe that the risk of taking HMPs during pregnancy is not high. However, we share the view of other authors that intake of HMPs during pregnancy carries potential risks and should not be taken without adequate medical indications.

A question raised is the risk of intrauterine growth restriction after the intake of HMPs and / or WPPs. In the present study, the mean birth weights were 3046 g and 2978 g in the two groups, respectively, there being no statistically significant difference between them. A study by Fok et al[16] found the mean birth weight at term was 2997 g (standard deviation, 407 g) for the general population in Hong Kong.

Given that in the present study, the fetal risks after intake of HMPs or WPPs were not high, whether all such women should have prenatal testing is arguable. However our current database is not large enough to allow us to confidently infer that there is really no increase in the prevalence of fetal abnormalities. In our current practice, HMP or WPP users are referred to the prenatal diagnostic clinic, if a medication which they took is associated with adverse effects on pregnancy (inferred from a literature search). On the other hand, if a medication is known to be safe in pregnancy, a referral is not required. If there were no data in the literature, the decision on a referral was individualised. Risk factors other than drugs and maternal anxiety were also taken into consideration.

The number of 'drugs' taken were greater in the WPP group (mean, 2.5 per subject) than the HMP group (1.5 per subject). These data nevertheless need to be interpreted with caution, since even one dose of a HMP could in fact consist of many active components.

More women in the WPP group were nulliparous compared to the HMP group; the mean age of the former being smaller than the latter. One postulation could be that younger women received a western education and

hence more readily chose WPPs.

There are limitations to the present study. The number of HMP users was not large. Under-reporting was possible, as the reported prevalence of HMP users was higher among Chinese in mainland and Taiwan than what we encountered. Besides, it is important to note if there is any association between specific HMPs and specific fetal anomalies. This will not be easy if the number of HMP users is small and the prevalence of fetal anomalies is low. Collaboration among different centres may help.

In conclusion, our data showed that after the intake of HMPs or WPPs, the risk of fetal abnormalities was not higher than that in the general unexposed population. There was also no demonstrable increase in the risk of fetal growth restriction or silent miscarriages in either group. Whether to refer all pregnant HMP or WPP users to the prenatal diagnostic clinic appears questionable.

References

1. Lacroix I, Damase-Michel C, Lapeyre-Mestre M, Montastruc JL. Prescription of drugs during pregnancy in France. *Lancet* 2000; 356:1735-6.
2. Hemminki E, Mäntyranta T, Malin M, et al. A survey on the use of alternative drugs during pregnancy. *Scand J Soc Med* 1991; 19:199-204.
3. Ernst E. Herbal medicinal products during pregnancy: are they safe? *BJOG* 2002; 109:227-35.
4. Gharoro EP, Igbafe AA. Pattern of drug use amongst antenatal patients in Benin in City, Nigeria. *Med Sci Monit* 2000; 6:84-7.
5. Mabina MH, Pitsoe DB, Moodley J. The effect of traditional herbal medicines on pregnancy outcome. The King Edward VIII Hospital experience. *S Afr Med J* 1997; 87:1008-10.
6. Pastore L. Home remedies used during pregnancy. *The Cochrane Library* 2000; 3:529.
7. Chuang CH, Hsieh WS, Guo YL, et al. Chinese herbal medicines used in pregnancy: a population-based survey in Taiwan. *Pharmacoepidemiol Drug Saf* 2007; 16;464-8.
8. Henry A, Crowther C. Patterns of medication use during and prior to pregnancy: the MAP study. *Aust N Z J Obstet Gynaecol* 2000; 40:165-72.
9. Splinter MY, Sagraves R, Nightengale B, et al. Prenatal use of medications by women giving birth at a university hospital. *South Med J* 1997; 90:498-502.
10. Donati S, Baglio G, Spinelli A, Grandolfo ME. Drug use in pregnancy among Italian women. *Eur J Clin Pharmacol* 2000; 56:323-8.
11. Aviv RI, Chubb K, Lindow SW. The prevalence of maternal medication ingestion in the antenatal period. *S Afr Med J* 1993; 83:657-60.
12. Palinkas LA, Kabongo ML; San Diego Unified Practice Research in Family Medicine Network. The use of complementary and alternative medicine by primary care patients. A SURF*NET study. *J Fam Pract* 2000; 49:1121-30.
13. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States; 1990-1997: results of a follow-up national survey. *JAMA* 1998; 280:1569-75.
14. Leung KY, Lee YP, Chan HY, et al. Are herbal medicinal products less teratogenic than Western pharmaceutical products. *Acta Pharmacol Sin* 2002; 23:1169-72.
15. Leung WC, Lee CP, Tang MH. Evaluation of routine obstetric ultrasound examination in detecting fetal structural abnormalities in low risk pregnancies. *Hong Kong J Gynaecol Obstet Midwifery* 2000; 1:28-32.
16. Fok TF, So HK, Wong E, et al. Updated gestational age specific birth weight, crown-heel length, and head circumference of Chinese newborns. *Ach Dis Child Fetal Neonatal Ed* 2003; 88:F229-36.