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Evaluating the safety of St. John's Wort in human pregnancy

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ABSTRACT

St. John's Wort is a herbal therapy, shown to be effective in treating mild to moderate depression; a disease common in women in their childbearing years. With a significant proportion of unplanned pregnancies, exposure to St. John's Wort into pregnancy is expected to occur. The purpose of this study was to determine whether exposure to this agent in pregnancy is associated with major malformations. We prospectively collected and followed subjects taking St. John's Wort and compared them to a matched group of pregnant women taking other pharmacologic therapy for depression and a third group of healthy women, not exposed to any known teratogens. We obtained follow-up information on 54 St. John's Wort exposed pregnancies and 108 pregnancies in the two comparator groups. Our results indicated that the rates of major malformations were similar across the three groups, with 5%, 4% and 0% in the St. John's Wort, disease comparator, and health group, respectively ($p = 0.26$), This was not different that the 3–5% risk expected in the general population. The live birth and prematurity rates were also not different among the three groups. Though further large scale studies are still needed, this first study on the effects of St. John's Wort in human pregnancy does provide some evidence of fetal safety.

1. Introduction

The use of complementary and alternative medicine (CAM) is on the rise, [1–3] with herbal supplements as one of the fastest growing segment of the dietary market in the US [4]. Surveys have shown that women are frequent users of CAM [2,5,6] and continue to use such therapies during pregnancy and lactation despite a lack of evidence for safety.

One of the most prevalent herbals on the market, St. John's Wort, *Hypericum perforatum* L., has been used for its medicinal properties for hundreds of years for a variety of ailments. As the second best selling herb in the US, St. John's Wort has experienced significant growth in its market share [4,7]. Most recently it has gained attention in the treatment of depression. At least ten active constituents of St. John's Wort have been identified. Current evidence from studies in humans, suggests that at least two constituents, hypercin and hyperforin, play a significant role in its pharmacologic effect in the treatment of depression [8–10]. I. Studies have shown that extracts of St. John's Wort inhibit serotonin re-uptake [11–13] and antagonize the serotonin ($5HT_3$ and $5HT_4$) receptors [9]. Numerous clinical trials and at least three meta-analyses [14–16] were conducted, some of them showing St. John's Wort to be superior to placebo in the treatment of mild to moderate depression.

The safety of using St. John's Wort during pregnancy is an important topic to consider, in part, because women in their reproductive years are frequent users of natural health products [2,17], and because at least half of all pregnancies are unplanned [18].

A number of animal studies investigated St. John's Wort and its effect on pregnancy and offspring. A study in rats [19], using doses up to 25 times the recommended human dose throughout gestation and lactation, was unable to show any neurobehavioral or developmental effects on the offspring. Maternal weight gain or length of gestation, likewise, was not affected. Two other studies in mice showed no significant impact on cognition [20] or behavioral tasks [21]. In these studies, the doses used were equivalent to human therapeutic doses, based on body surface area, and were shown to affect rodent behaviour typically evaluated when assessing for antidepressant effects. A fourth animal study [22], also conducted in mice, showed no increased risk for structural anomalies and similar pup length and head circumference in the exposed and unexposed groups. Male exposed offspring were slightly lower in birth weight than the unexposed controls but this difference was no longer evident by postnatal day 3. The negative animal studies are reassuring, in that they do not suggest structural or functional deficits attributable to St. John's Wort exposure during gestation. However, since animals and humans may not respond in the same manner to potential toxins, studies in humans are required to rule out potential fetal effects.

To date, no human studies have examined the effects of St. John's Wort during pregnancy. Grush et al. [23] reported on two women

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who took St. John's Wort in their pregnancies to avoid the use of conventional synthetic medications. No apparent adverse outcomes were noted.

The primary objective of this study was to determine the risk for major congenital malformations following maternal exposure to St. John's Wort in pregnancy. We also compared birth weights and examined the risk for other adverse pregnancy outcomes, such as prematurity.

2. Methods

The safety of St. John's Wort in pregnancy was assessed using a prospective, observational, controlled cohort design. The sample group, both exposed and unexposed subjects, was drawn from women who contacted the Motherisk Program, a teratogen information service in Canada. The exposed index group consisted of women who used St. John's Wort at any time during their pregnancy. The exposed index patients were compared to a disease-matched group of women with depression who were using conventional pharmacologic treatments for their disease. A second comparator group of healthy women not exposed to any known teratogens was also included. Healthy comparators called the service in early pregnancy but were not exposed to any known teratogens. Both comparator groups were matched to their exposed counterpart by gestational age at intake (±2 weeks), maternal age (±2 years), and gravidity.

At initial contact with the patient, during pregnancy, detailed information on the use of medications, medical and obstetric history and other exposures was recorded. A second contact with the patient was made after the expected date of delivery to collect further information about additional exposures, medical conditions and details about delivery and infant outcomes. When possible, the Center for Epidemiologic Studies Depression Scale (CES-D) [24] was be used to establish depressive symptomatology in all patients, both at the initial, as well as during the follow-up interview. The CES-D is a 20 question depressive symptom screening tool based on patient self-report. All interviews were conducted systematically and data recorded on structured standardized collection forms. Interviews were conducted in the same manner for both exposed and unexposed subjects. Subjects were recruited and followed over a 5–7 year time interval. Patients were excluded if they were unable or unwilling to complete the interviews in English. Women in the healthy comparator group were excluded from participation if they had any chronic underlying diseases before the onset of pregnancy detected during either interview.

Table 2
Characteristics of patients using St. John's Wort in pregnancy.

	Count (%)
Trimester of exposure	
T1	42 (76%)
T1 + T2	3 (5.5%)
Entire pregnancy	4 (7.3%)
T2, T3 or T2 + T3	5 (9.1%)
Indication	
Depression/anxiety	39 (72.2%)
Pain	3 (5.5%)
Improve mood/energy	4 (7.3%)
Sleep	3 (5.5%)
PMS	2 (3.6%)
Other	3 (5.5%)
Patient reported St. John's Wort effective	36 (65.5%)

Categorical data, such as rates of major malformations was compared using the chi square test (χ^2). Continuous data was compared using Analysis of Variance (ANOVA) for data that was normally distributed and ANOVA on ranks was used for non-normally distributed data.

3. Results

We were able to successfully follow 54 pregnancies exposed to St. John's Wort and consequently 108 comparator pregnancies. There were no differences in baseline characteristics among the three groups of patients (Table 1) Among the St. John's Wort cases 49 were exposed at least during the first trimester (Table 2). Their average daily dose as reported by the patients was 615 mg among those using tablets. A small number of subjects for whom doses could not be estimated, took St. John's Wort in the form of teas (3), tincture (1) or granules (1). Women taking St. John's Wort reported doing

Table 1
Characteristics of women exposed to St. John's Wort (SJW) during pregnancy and their disease and healthy comparators.

Characteristic	SJW-Exposed ($n = 54$)	Disease[a] ($n = 54$)	Healthy non-exposed ($n = 54$)	p-value
Age (years ± SD)*	32.6 ± 5.3	32.5 ± 5.0	32.5 ± 4.9	0.99
Gravidity (%)†				
1	12 (22.2)	12 (22.2)	17 (31.5)	
2	26 (48.1)	21 (38.9)	22 (40.7)	
≥3	15 (27.7)	21 (38.9)	15 (27.7)	0.81
Parity (%)†				
0	20 (37.0)	16 (29.6)	23 (42.6)	
1	27 (50)	26 (48.1)	25 (46.3)	
≥2	7 (13.0)	12 (22.2)	6 (11.1)	0.76
Previous miscarriage (%)†				
0	43 (79.6)	44 (83.0)	42 (77.8)	
1	7 (13.0)	7 (13.0)	7 (13.0)	
≥2	4 (7.4)	2 (3.8)	5 (9.2)	0.86
Previous elective abortions (%)†				
0	48 (88.9)	47 (87.0)	49 (90.7)	
≥1	6 (11.1)	7 (13.0)	5 (9.3)	0.65
Gestational age at call (weeks ± SD)‡	10.9 ± 9.7	9.3 ± 6.8	11.3 ± 9.9	0.44
CES-D score in pregnancy§	12.5 ± 12.5	17.3 ± 11.8	8.7 ± 6.8	<0.001
Smoking†				
No	48 (88.9)	52 (96.3)	50 (92.6)	
Yes	8 (11.1)	2 (3.7)	4 (7.4)	0.27
Alcohol†				
None	48 (88.9)	54 (100)	52 (96.3)	
Light	6 (11.1)		2 (3.7)	0.02

* One-Way ANOVA.
† Chi square test.
‡ One-Way ANOVA on Ranks.
§ Available for 59% of subjects.
[a] Medications used by disease group included paroxetine (19), venlafaxine (14), citalopram (12), fluoxetine (3), sertraline (3), polytherapy (2), moclobemide (1).

Table 3
Pregnancy outcomes among women expose to St. John's Wort (SJW) in pregnancy and their comparator groups.

Characteristic	SJW-Exposed ($n=54$)	Disease ($n=56$[a])	Healthy non-exposed ($n=56$[b])	p-value
Fetal outcome[c]				
Livebirth	43 (79.6%)	48 (85.7%)	51 (91.1%)	
Spontaneous abortion	11 (20.3%)	7 (12.5%)	5 (8.9%)	
Elective abortion	0	1 (1.8%)	0	0.28
Gestational age at birth (weeks ± SD)[d]	39.4 ± 2.1	39.0 ± 2.8	38.9 ± 2.1	0.35
Delivery[c]				
Vaginal	35/42 (83.3%)	33/45 (73.3%)	39/47 (83.0%)	
Cesarean section	7/42 (16.7%)	12/45 (26.7%)	8/47 (17.0%)	0.41
Preterm delivery				
No	41/43 (95.3%)	31/39 (79.5%)	39/45 (86.7%)	
Yes	2/43 (4.7%)	8/39 (20.5%)	6/45 (13.3%)	0.10
Birth weight (g ± SD)[e]	3566 ± 590	3443 ± 518	3452 ± 552	0.51
Sex[c]				
Male	22 (51.1%)	25 (52.1%)	31 (60.8%)	0.57
Post-Partum CES-D score[d,f]	7.0 ± 6.9	11.3 ± 8.3	8.5 ± 8.4	0.18
Fetal malformations[c]				
Yes	2/38[g] (5.3%)	2/48[h] (4.2%)	0	0.26

[a] Including 2 twin pregnancies.
[b] Including 1 triplet pregnancy.
[c] Exact methods.
[d] One-way ANOVA on ranks.
[e] One-way ANOVA.
[f] Available for 47% of subjects.
[g] Offspring malformations are reported in the St. John's Wort group as a proportion of first trimester exposures that were liveborn (1 obstructed ureter and 1 hypospadias).
[h] Offspring malformations in the disease matched cohort included 1 plagiocephaly and 1 esophageal atresia with tracheoesophageal fistula.

so primarily for the treatment of depression. Seven of the exposed women continued St. John's Wort into the second or third trimester and five used the therapy only in the second or third trimester of pregnancy.

CES-D scores in the pregnancy, available for 59% of subjects, were found to be significantly higher in the disease group than compared to the healthy comparator ($p<0.001$). The St. John's Wort exposed women also had CES-D scores slightly higher than the healthy group though this did not reach statistical significance (Table 1).

Pregnancy outcomes were similar in the three cohorts (Table 3). There were 43 live births in the St. John's Wort group with a mean birth weight of 3566 g. The live birth rate and other pregnancy outcomes in the disease and healthy comparator groups were similar. The comparator groups had some multiple gestations, namely twins and triplet pregnancies. Because such pregnancies would be at risk for adverse outcomes they were subsequently removed in a post hoc analysis. When the three groups were reanalyzed, without multiple gestations, all pregnancy outcomes remained non-significant. There were 3, 2, and 0 malformations in the St. John's Wort, disease comparator and healthy comparator groups respectively. Among women using St. John's Wort 36 (67%) reported that they were satisfied that the product treated them effectively. After pregnancy the CES-D scores, available in 47% of subjects, did not reveal any difference in depression status between the three groups. ($p=0.18$, Table 3).

4. Discussion

A general trend for women and the population at large to gravitate towards increased CAM use as well as an overall lack of data on the safety of herbal medications has created a tremendous need for studies in this area of medicine. St. John's Wort has been of particular interest because evidence suggesting it may be efficacious in the treatment of some forms of depression has emerged. Women are at most risk for depression during their reproductive years [25,26] and determining the safety of appropriate treatments in pregnancy is imperative.

In designing this study we collected a disease comparator group in order to control for possible confounding of outcome by indication, namely depression. Our findings show that women in all three groups had similar outcomes. Both the disease group and the St. John's Wort subjects had higher rates of spontaneous abortions. Though the proportions were larger in the St. John's Wort group than the other two, these differences did not reach statistical significance. While there are no known reports of an association between St. John's Wort and spontaneous abortion, there is some evidence of increased rates of spontaneous abortions among women with depression in pregnancy [27,28] and as such a disease effect should be considered. The rates of major malformations and other adverse pregnancy outcomes were not increased and malformations rates were similar to those expected in the general population. Since we did not examine the offspring ourself we were limited in our ability to collect information about minor malformations in this cohort. It is unlikely that mothers would inaccurately report major malformations however.

Of note, when possible, we measured CES-D scores on women in the three groups. Analysis of the depression scores showed that women in the disease comparator scored significantly higher than the healthy group. There were no other statistically significant between group differences; however the mean CES-D scores of the St. John's Wort exposed patients was between the means of the other two groups. This suggests that the patients using St. John's Wort were perhaps less likely to have depression or had a less severe form of depression and may represent a slightly different patient population than those women on traditional antidepressants. It is also possible that the treatment played a role in these scores, that is, the St. John's Wort patients were adequately treated while the patients on traditional antidepressants may have been receiving suboptimal pharmacotherapy. Nevertheless, most of the St. John's Wort subjects had discontinued treatment by the third trimester, yet their post-partum scores remained lower than the disease group. Postpartum differences between groups were no longer statistically significant, however the disease group continued to have higher CES-D scores than the other two groups of subjects. We did

not continue to follow these subjects beyond the initial postpartum period and did not examine impacts on breastfeeding rates or the safety of this agent during lactation. Though most women chose to breastfeed in this cohort, none of them reported continuing St. John's Wort while lactating. However, other investigators from our group have previously reported on breastfeeding women using SJW during lactation [29].

Our study was limited by its small sample size. Considering the nature of the population from which the subjects were drawn this may not be surprising. Women contact our service in early pregnancy inquiring about available information on the safety of medications in pregnancy. Many of these patients had not yet begun treatment and when study recruitment interviews were conducted the vast majority of patients chose not to take St. John's Wort, citing lack of safety information. Moreover, patients contacting the Motherisk program may represent a select population with health seeking behaviours different from the population at large. It is likely then, that they would have more favorable pregnancy outcomes then those patients who would not choose to contact our service. These differences highlight the tremendous need for data on the use of drugs in pregnancy for all women. A lack of information leads to fears and inappropriate or nonexistent treatment for this very vulnerable population.

This is the first human study investigating the use of St. John's Wort in pregnancy. Although more data is certainly needed, infants exposed in utero to St. John's Wort did not appear to do worse than the offspring of either the healthy controls or the disease comparator groups. This can be reassuring to the many women who may have inadvertently been exposed to or chose to continue to take St. John's Wort in pregnancy.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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