EDITORIAL

Spontaneous miscarriages in patients with bladder pain syndrome/interstitial cystitis - effect of stress on inflammation?

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Interstitial cystitis/painful bladder syndrome (IC/PBS) affects mostly women and is characterized by pelvic pain or pressure and frequency of voiding in the absence of urinary tract infection. Acute stress worsens IC/PBS symptoms and bladder inflammation associated with increased number of activated mast cells. We investigated retroactively the incidence of spontaneous miscarriages and any related stress in IC/PBS patients. A questionnaire was posted on an IC/PBS website and patients visiting the site were invited to complete and file it electronically. Limitations include the lack of defined diagnosis those responding, and of a validated stress questionnaire. There were 193 respondents (mean age = 37.3 years) over two weeks. Of those responding, 87% (mean age = 33.2 years) had received a diagnosis of IC/PBS. Of those respondents with IC/PBS, 76% reported having had miscarriages: (a) 55% had one miscarriage, (b) 26% had two, and (c) 23% had three or more. These rates are much higher than those of in the general population: 10-20% with one and 1-2% with habitual spontaneous miscarriages. The majority of patients (78%) reported experiencing significant stress. IC/PBS patients appear to have a much high incidence of spontaneous miscarriages compared to the general population. Most patients reported experiencing stress that has been associated with miscarriages. This finding may be explained via stress stimulating bladder and uterine immune cells, especially mast cells, inhibition of which by the natural flavonoid quercetin may be beneficial.

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a disorder of the urinary bladder affecting mostly women and characterized by chronic pelvic pain, frequency and nocturia (1, 2). As IC/PBS has become better known and the diagnostic criteria do not necessarily include cystoscopy under spinal or general anesthesia, the prevalence has increased to about 1% of female patients (1). IC/PBS pathogenesis appears to be multifactorial (3, 4) and has been considered a neuro-immuno-endocrine disorder (5) associated with variable degrees of bladder inflammation (6) and bladder mastocytosis (7).

Acute stress was shown to worsen chronic pelvic pain and also worsened bladder-related symptoms in humans (8). Psychological stress has also been associated with infertility (9). The effect of stress

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on miscarriages in IC/PBS has not been investigated and could be higher than in the general population given the evidence of inflammation in the pelvic area. A number of studies have reported increased risk of pregnancy loss associated with psychological stress (10, 11).

Mast cells were increased by more than 10-fold in deciduas in miscarriages (12). Mast cells are essential for allergies (13), but also inflammation (14) by releasing histamine, tryptase, proteoglycans, prostaglandin D_2, leukotriene C_4 and several pro-inflammatory cytokines and chemokines (15, 16). The decidua of women with high levels of stress were reported to have a significantly high number of mast cells positive for their unique proteolytic enzyme, tryptase (10).

Here, we report preliminary findings indicating that spontaneous miscarriages are more frequent in IC/PBS patients than in the general population, and may be associated with antecedent stress.

MATERIALS AND METHODS

A 25-item questionnaire (Table I), which included questions on demographics, medical diagnosis, spontaneous miscarriages and stress, was made available on a website visited by IC/PBS patients (IC-network.com). The survey was posted for three months on http://www.keysurvey.com/. This was an information gathering questionnaire and was not designed to diagnose any disease or quantitate symptoms. No personal information was collected and no HIRB approval was required.

The results are presented as percentage of IC/PBS patients who answered a particular question. Each question is presented in the results. No statistics were applied.

Findings

A total of 193 surveys were returned. The mean age of the responders was 37.3 years, with a mean age of IC/PBS diagnosis being 33.2 years. Of all the respondents, 87% were diagnosed with IC/PBS (Fig. 1A) and 76.7% of them reported having had miscarriages (Fig. 1B). The actual breakdown was as follows: (a) 79 patients (55%) had one miscarriage, (b) 38 patients (26%) had two miscarriages, and (c) 33 patients (18%) had three or more miscarriages (Fig. 1C).

At the time of miscarriage, 8.1% of subjects were 19 years old or younger, 65% were 20-29 years old, 25.7% were

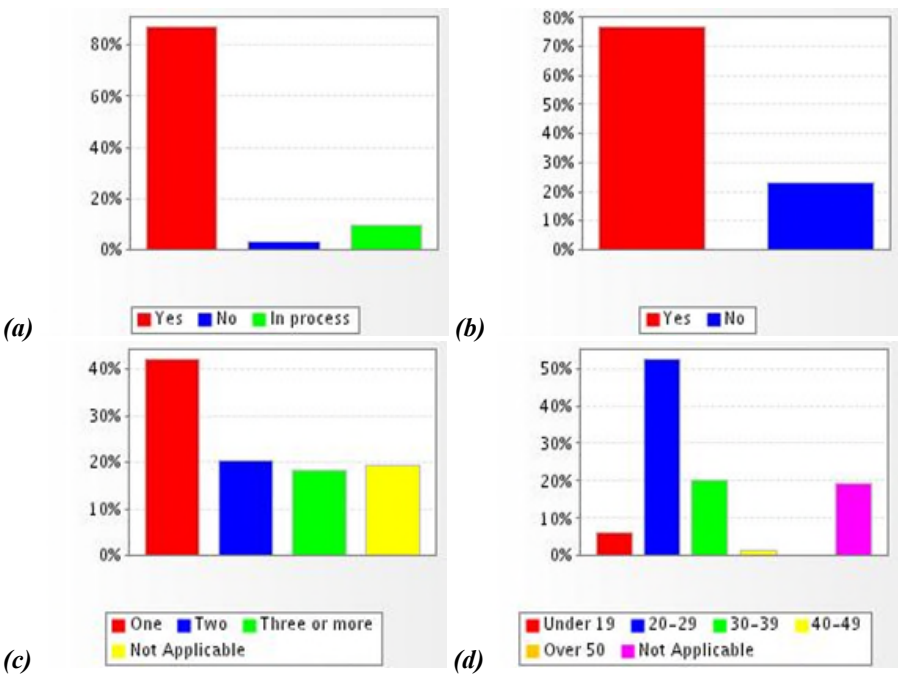

Fig. 1. *The number of BPS/IC patients who reported any miscarriage.* ***a)*** *Have you been diagnosed with IC?* ***b)*** *Have you experienced a miscarriage?* ***c)*** *How many miscarriages have you had?* ***d)*** *How old were you when the miscarriage(s) occurred?*

30-39 years old, and 2% were 40-49 years old (Fig. 1D).

Most responders (57.1%) reported that they had experienced the miscarriage after they developed bladder symptoms (Fig. 2A) and 18.5% after they were diagnosed with IC/PBS (Fig. 2B). The miscarriage was attributed to a genetic or medical condition in less than 10% responders (Fig. 2C). About 42% of responders indicated that they succeeded in having a child eventually (Fig. 2D).

There were four different questions relating to stress. In the first, 25.9% of responders indicated that their miscarriage was associated with an event or period of stress (Fig. 3A). However, almost 80% replied that they had been upset during the last month because of something that had happened unexpectedly (Fig. 3B) and 37.8% indicated they were upset about 50% of the time; 31.1% indicated they were fairly anxious often and 10% very often. Over 71% indicated that during the last month they had felt unable to control the important things in their lives (Fig. 3C). Finally, over 85% reported that they had felt nervous or stressed during the last month, with 57.2% indicating they did so very often (Fig. 3D).

DISCUSSION

The present findings suggest that IC/PBS patients may have a higher incidence of spontaneous miscarriages than the general population. The incidence of one spontaneous miscarriage in IC patients (mean age 33.2 years) was 76.7%, compared to 13.5% in the general population and 8.9% in the age group of 20-24 years (17). The incidence of habitual spontaneous miscarriages (3 or more) was about 23% in IC/PBS patients, compared to 1-2% in the general population (18). A miscarriage after bladder symptom flare-up occurred in 57.1% responders and 18.5% had a miscarriage after IC/PBS diagnosis.

Many IC/PBS patients also experience anxieties (19) and panic disorder (20). The symptoms of IC/PBS are exacerbated by physical or emotional stress (14, 21). A common link between IC/PBS, stress and spontaneous miscarriages may be the mast cells, which are increased and activated in the bladder of

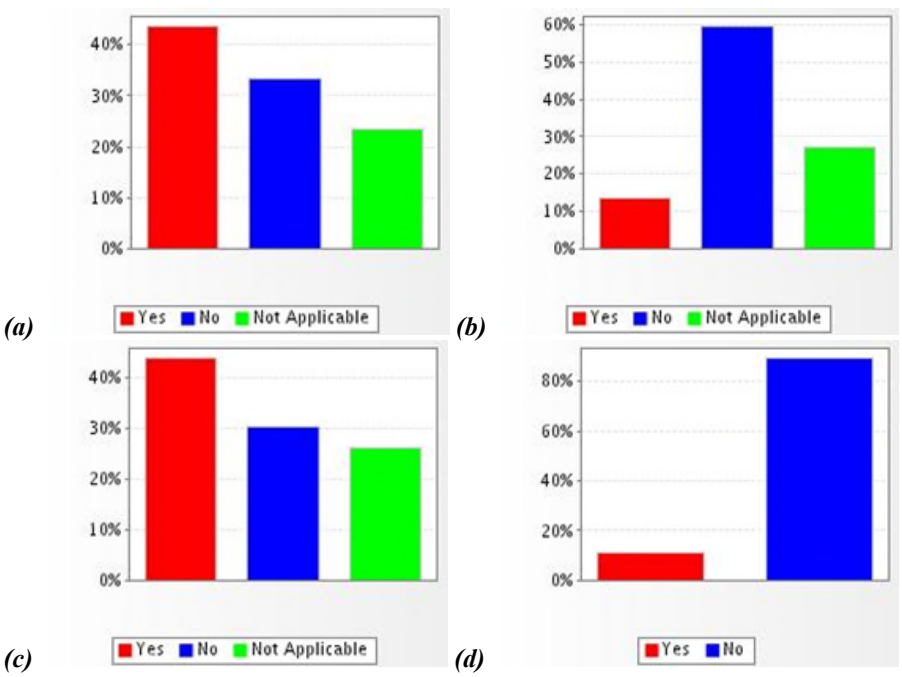

Fig. 2. *Factors that may have contributed to the miscarriages.* ***a****) Did your miscarriage occur after you developed bladder symptoms?* ***b****) Did your miscarriage occur after you were diagnosed with BPS/IC?* ***c****) Have you successfully had a child after miscarriage?* ***d****) Was your miscarriage associated with or attributed to any genetic or medical condition?*

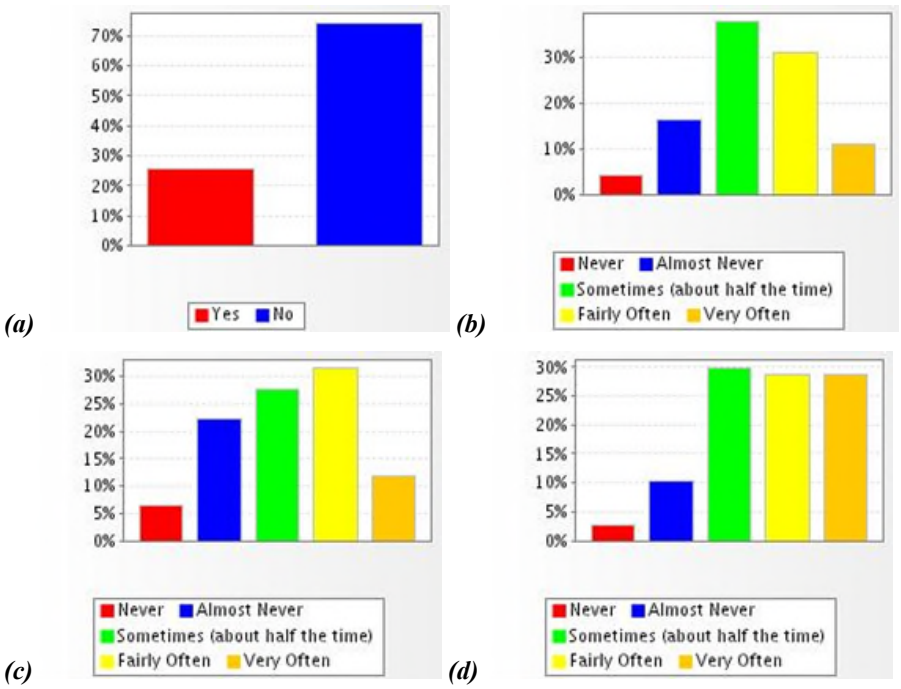

Fig. 3. *Association of miscarriages with stress.* ***a)*** *Was your miscarriage associated with any event or period of stress?* ***b)*** *In the last month, how often had you been upset because of something that happened unexpectedly?* ***c)*** *In the last month, how often had you felt that you were unable to control the important things in your life?* ***d)*** *In the last month, how often had you felt nervous or "stressed"?*

IC/PBS patients (7, 22), and could be triggered by acute stress (23, 24). Systemic or pelvic stressful conditions may increase the incidence of spontaneous miscarriages in IC/PBS patients by inducing the local release of corticotropin-releasing hormone (CRH) or other neuropeptides, such as substance P (SP), which then activate bladder and/or endometrial mast cells. For instance, bladder mast cells are closely associated with SP-positive neurons (25) and respond to SP with release of histamine, cytokines and chemokines (14). We reported high CXCL8 level in subjects with habitual spontaneous miscarriages (26) and CXCL8 was significantly increased in the plasma of women with second trimester miscarriage (27).

Most subjects reported being chronically stressed with 25% indicating the presence of a stressful period associated with the miscarriage. Psychological stress has been associated with preterm delivery and spontaneous miscarriages (10, 28), including recurrent miscarriages (29). In one study, spontaneous miscarriages at about 11 weeks of gestation were strongly associated with more stressful episodes than other gestational periods (30). Another study reported more than two-fold increase in the rise of spontaneous miscarriages in the presence of psychological stress. (28) A systematic review and meta-analysis concluded that the risk of miscarriages was significantly higher in women with a history of psychological stress (31).

Maternal stress due to environmental and/or socioeconomic factors was also linked to preterm delivery and was associated with high levels of CRH secreted under stress (32). In addition to its release from the hypothalamus, CRH is also released in local tissues, where it induces pro-inflammatory effects through mast cell activation (14). Moreover, human mast cells (33) and endometrium (34) can produce CRH, which can stimulate prostaglandin production in uterine tissues, leading to parturition (32). We reported high levels of CRH and tryptase in products of conception from women with habitual spontaneous miscarriages (26).

This study has a number of limitations. The response rate may bias the outcome and overestimate

the percent of patients who had miscarriages because those who did not would be less motivated to take the survey. The questions about whether miscarriage was associated with an event or period of stress are subjective and may be influenced by recall bias. The wording of the question concerning the association of stress and miscarriage may had been misleading.

Implications

The present preliminary findings raise the issue that psychological stress may contribute to spontaneous miscarriages due to stimulation of bladder and uterine mast cells in patients with IC/PBS. Inhibition of mast cells by the natural flavonoid quercetin, especially in a liposomal formulation to increase oral absorption, could provide some degree of protection (35).

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