



Reproductive experience of women living with phenylketonuria

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ABSTRACT

Introduction: Many women with PKU are well-informed about the risks of maternal PKU but there are several barriers to achieving satisfactory metabolic control before and during pregnancy. Many studies have documented the outcome of maternal PKU infants, but very little has been reported about the experiences of women of reproductive age with PKU, particularly about their psychosexual development, pre-conception, pregnancy and postnatal experience.

Methods: In the UK, in a subsection of an online questionnaire conducted by the National Society for PKU (NSPKU) about living with PKU, women aged 18 years and over completed 9 closed questions about their pre-conception, pregnancy and post-natal experiences and an open-ended question on their reproductive health.

Results: 300 women aged 18 years and over with PKU completed this questionnaire with 37% ($n = 111/300$) of women already having children. 56% ($n = 71/128$) of pregnancies were planned and a further 18% ($n = 23/128$) of women had both planned and unplanned pregnancies. Most women (73%, $n = 200/273$) expressed concerns, fears and distress about pregnancy and two thirds of women who had at least one pregnancy stated that having PKU made pregnancy more stressful and difficult. 60% ($n = 164/273$) were concerned that they may cause harm to a baby, 58% ($n = 159/273$) worried about their ability to manage a strict diet during pregnancy, 54% ($n = 147/273$) had anxiety about their ability to maintain blood Phe within target range, and 48% ($n = 132/273$) feared having an unplanned pregnancy.

Postnatally, 48% ($n = 45/93$) had low mood or sadness, 41% ($n = 38/93$) were depressed, 34% ($n = 32/93$) felt unable to cope, 33% ($n = 31/93$) said they could not manage their PKU and care for their baby, 14% ($n = 13/93$) struggled with child care needs and 4% ($n = 4/94$) worried they might hurt themselves or their baby through being unable to manage their diet.

Conclusions: Many women with PKU have unmet sexual and reproductive health needs. Pregnancy fears are prominent from adolescence onwards and for some women overarching concerns about their ability to cope with pregnancy led to a decision not to have children. Interventions are needed to reduce the psychological impact of the risk of maternal PKU syndrome and assist with safe pregnancies. Post-natal experiences of women with PKU give rise to concern.

1. Introduction

In maternal phenylketonuria (PKU), high blood phenylalanine (Phe) levels during pregnancy have a teratogenic effect on the developing foetus which can result in intrauterine growth retardation, facial dysmorphism, developmental delay, intellectual disabilities, microcephaly and congenital heart disease (CHD) [1–7]. Strict metabolic control before and throughout pregnancy reduces foetal risk if dietary control is achieved before conception and maintained throughout pregnancy [8]. The European PKU Guidelines [9] state that treatment should commence pre-conception for maternal PKU and it emphasises that

significant effort should be undertaken to avoid any unplanned pregnancies.

In women with PKU, much importance is placed on education and effective contraceptive methods so that women are in control of their reproductive health and avoid unplanned pregnancies. The European Guidelines [9] emphasise that all women with PKU of child-bearing age, starting at menarche, must receive preconception counselling about the risks of an unplanned pregnancy. They should receive detailed counselling regarding family planning and understand the adverse effects on the foetus of elevated Phe levels. Education should continue into adulthood. For teenage girls and women, it is likely to be

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discussed at most PKU clinic appointments.

The dietary regimen pre-conception and during pregnancy is rigorous. Women initially commence a very strict low Phe diet, consume a low Phe synthetic protein substitute three times daily, small, measured quantities of natural protein according to tolerance, maintain adequate energy intake to avoid catabolism (but need to avoid excess weight gain), and monitor blood Phe levels at least twice weekly to maintain concentrations between 120 and 360 $\mu\text{mol/L}$ [4,9–12]. Women usually attend a PKU clinic with experience of managing PKU. If women fail to establish metabolic control in pregnancy, there is a National Health Service (NHS) England commissioning policy that permits the use of the drug sapropterin [13]. Sapropterin dihydrochloride, a synthetic formulation of tetrahydrobiopterin (BH_4) acts as a cofactor for phenylalanine hydroxylase (PAH), increasing its activity by stabilisation of the PAH tetramer [14]. It is effective in 20 to 50% of patients, usually with mild or moderate phenotype; and it may increase daily Phe tolerance by two to three fold and improve metabolic control [9]. For women who are sapropterin responsive and struggling with dietary management and metabolic control, it should help alleviate some of the management burden. Unfortunately, the NHS policy only permits testing with sapropterin at the time of pregnancy and the drug must stop at the end of pregnancy.

Many women with PKU are well-informed about the risks of maternal PKU but there are several barriers to achieving satisfactory metabolic control before and during pregnancy. The current policy of maintaining dietary therapy throughout life may improve intellectual functioning and alleviate some of the difficulties that women encounter in returning to a low Phe diet. However, they are still likely to have higher blood Phe levels than are considered safe at the time of pregnancy if not on a strict pre-conception diet first. Some women may have stopped or liberalized their diet in adulthood and may have difficulties resuming a low Phe diet and tolerating the protein substitute [15].

Many studies have documented the outcome of maternal PKU infants, but very little has been reported about the experiences of women of reproductive age with PKU particularly about psychosexual development, the pre-conception period, during pregnancy and postnatally. A questionnaire that was developed by the UK National Society for PKU (NSPKU) for patients and carers of children with PKU contained a subsection specifically written for women aged 18 years and over. We report the results of this survey for women only.

2. Material and methods

An online questionnaire was voluntarily completed and submitted by adults with PKU or parents/caregivers of children or adults unable to complete the survey themselves. The survey was placed on the UK NSPKU website, facebook and twitter account between 9th November 2017 to 31st January 2018. Additional promotion of the questionnaire was conducted by the NSPKU at patient and family meetings. Only one questionnaire was completed for each person with PKU.

The questionnaire was comprised of 61 questions, including single choice, multiple choice and 4 open-ended questions on all aspects of PKU. In a subsection of the questionnaire, women aged 18 years and over completed 9 closed questions on pre-conception, pregnancy and post-natal pregnancy experience and the following open-ended question:

If there is anything else about your experience of being a woman with PKU that you would like us to know and include? (Your answer may be included in published materials but you will not be identified by name.)

The survey dataset was imported into 'NVIVO v 11 pro' software, a programme for qualitative data analysis. There were 77 useable responses, and each one was created as a case in NVIVO (allowing responses to be filtered by any characteristics or response which was captured in the survey). The open-ended question was created as a node, and the individual response within the question was read

separately and coded at a very fine level of detail according to one or more nodes created in response to emerging patterns in the data. Those responding to this question were considered a distinct group as they were questioned about experiences of being a woman with PKU and their reproductive health and generated a set of accounts of living with PKU in relation to fertility, pre-conception, pregnancy and post-natal experiences.

2.1. Data cleaning

Age breakdown was carried out as a check on the validity of the responses (i.e. to check that all responses were from adults) and compared against a separate question about their age.

2.2. Analysis

Data was analysed using descriptive statistics only. The verbatim extracts from the open questions were analysed using inductive thematic analysis [16] and NVIVO software. Recurring ideas, comments or patterns were coded in and organised into a hierarchical pattern of nodes with the top-level parent nodes being considered as themes. Codes and themes were reviewed and refined throughout the analysis process (e.g. merging and splitting codes).

2.3. Ethics

Ethical consent was not sought as patient identifiable data was not obtained. If names or hospitals were mentioned in verbatim abstracts, these were removed. The purpose of the questionnaire was explained in detail at the beginning of the document to respondents. It was clarified that the primary purpose of the document was to gain information to support NHS considerations of future PKU treatments options in England, Scotland, Wales and Northern Ireland. Potential respondents were also advised that the NSPKU may publish data from the survey. Women with PKU were considered to have given their consent by their voluntary completion and submission of the questionnaire online.

3. Results

Three hundred women aged over 18 years with PKU completed this questionnaire with 37% ($n = 111/300$) of women already having children (some had experienced more than one pregnancy). Fifty-six per cent ($n = 71/128$) of pregnancies were planned and a further 18% ($n = 23/128$) of women had both a planned and unplanned pregnancy. Fourteen percent ($n = 36/263$) of women had a miscarriage and 8% ($n = 21/263$) had more than one miscarriage.

Thematic analysis identified four themes: women's fears about pregnancy prior to pregnancy, diet during pre-conception and pregnancy, challenges in the post-natal period, and support required and information gaps.

3.1. Fears of pregnancy

Most women (73%, $n = 200/273$) completing the survey expressed concerns, fears and distress about pregnancy and two thirds of women stated that having PKU made pregnancy more stressful and difficult. Sixty per cent ($n = 164/273$) were concerned that they might cause harm to their baby if they became pregnant, 58% ($n = 159/273$) worried about their ability to manage a strict diet during pregnancy, 54% ($n = 147/273$) had anxiety about their ability to maintain blood Phe within target range, and 48% ($n = 132/273$) feared having an unplanned pregnancy. Many women (84%, $n = 93/111$) who had experienced pregnancy stated that they managed to maintain blood Phe levels within target range for most of the time and indicated that it was fear of damaging the foetus that influenced this level of control.

Some respondents expressed concern that as a woman with PKU it

may be unsafe for them to have a baby (39% $n = 107/273$), and some worried about the level of care they could provide for a baby (16%, $n = 43/273$). Eight per cent ($n = 22/273$) of women were too embarrassed to discuss pregnancy in clinic. Nine per cent ($n = 23/263$) of women said they had a pregnancy termination due to their PKU. From the results of the thematic analysis, it was evident that some women were so anxious about pregnancy and doing damage to the foetus or how they would cope with caring for a baby, that they chose not to have intimate sexual relationships. Some women stated they were unable to foster close personal relationships due to pregnancy fears. Many identified they needed psychological help to discuss the psycho-sexual aspects of PKU, but this support was often unavailable to them and they felt they could not share this with their medical team in a clinic environment. Also, the dichotomy of trying to reconcile maternal PKU with religious, cultural, ethical or moral beliefs relating to contraception and abortion was discussed.

Verbatim extracts from women's responses about their pregnancy fears (Theme: 'Fears of Pregnancy')

Pregnancy is a scary thought there is nothing I want more than to be a mum, but I am so scared about becoming pregnant and hurting my child or myself that I have never had sex as I'm so scared of there being an accident

I'm terrified about becoming pregnant when not on pre-con. I don't believe that I would ever be able to follow pre-con because I'm so bad at normal PKU diet. If I did have a child on pre-con, I'd worry at how I would cope with life, PKU and a baby. I can't cope with life on my own as it is now. I also worry at how my baby anxieties will affect my relationship as my partner is very keen to start a family. I am scared that I won't be able to follow pre-con, and this will have an effect on our relationship.

Fears about unplanned pregnancy has affected my ability to develop relationships in that way despite the knowledge that I can have a safe pregnancy if planned.

I think having been bombarded with information about pregnancy with PKU since around the age of 12, (quite rightly), it almost has put me off having children. However, I think this has been sub conscious. I had a couple of scares in my teens and early 20s, and it was awful worrying so much!! With this condition, I have always been very clear that I would seriously have to be desperate for a baby to go through it.

3.2. Experiences of dietary management pre-conception and during pregnancy

The low Phe diet was described as difficult by 78% ($n = 75/96$) of women in the pre-conception period and 59% ($n = 59/100$) during pregnancy.

This theme includes women's descriptions of their struggles with dietary management, particularly the pre-conception diet, which added to their stress of trying to conceive. During pregnancy some described their anxiety if they had severe morning sickness, particularly when it was prolonged and negatively impacted on metabolic control. Others described their difficulties in eating an adequate calorie intake or obtaining satisfactory supplies of low protein foods from their GPs. Many described that it was the fear of harming their unborn child that motivated them throughout pregnancy but then they described their joy at giving birth to a 'healthy' child. This was an achievement they were very proud of.

Verbatim extracts from women's responses about dietary management pre-conception and during pregnancy

Sticking to the PKU diet during pregnancy is not only extremely difficult but stressful too, I worry I can't eat enough and that the baby is going to be harmed because of that.

It is a shock to the system if you have not previously been on a strict diet to suddenly have to monitor. To try to get your head around protein amounts and making sure you stay within the levels as well as all other worries that come with pregnancy.

Fear motivated me to weigh and measure everything I drank and ate. I was directly responsible for the health of my child through the food choices I made. Determination made it possible.

Preparation is the key, I had 13 years of planning and forethought with my second. Surprise pregnancies are a little trickier, but motivation comes from the urge to protect. I had quite a high tolerance to start with, a good understanding of my diet and lots of support. I see other women on 0 exchanges struggle throughout their pregnancy and my heart goes out to them.

3.3. Post-natal challenges

In the post-natal period, 48% ($n = 45/93$) of women had low mood or sadness, 41% ($n = 38/93$) were depressed, 34% ($n = 32/93$) felt unable to cope, 33% ($n = 31/93$) said they could not care for their PKU as well as their baby, and 14% ($n = 13/93$) were unable to keep up with their child care needs. Four per cent ($n = 4/93$) worried that they might hurt themselves or their baby. Fourteen per cent ($n = 14/102$) said that health or developmental problems in their children were linked to PKU.

Women reported that in the post-natal period help from their health care team was reduced and they felt isolated and less supported. Many explained that they had no choice but to stop their low Phe diet as they could not juggle child care and dietary management. Many were often tired. Some struggled with breast feeding as they could not eat sufficient calories on a low Phe diet in order to sustain this. They identified how they needed more care from their health care providers at this vulnerable time in their life.

Verbatim extracts from women's responses about post-natal experiences

Everyone and everything else comes before me and my PKU even though it should be the other way around. In reality, my diet is the easiest thing to put to one side. My children, my husband, work, running around looking after everyone and everything. I cannot cope with the demands of day to day life and the time and emotional commitment needed to maintain good blood levels. I do have good support from my husband but that is not enough.

Went through a bad time after the baby was born had suicidal thoughts after the baby was born. Needed psychiatric help at the time and needed watching. Baby did have PKU.

It is a constant struggle to feed my family and then make a separate meal for me.

My diet as a busy working mum takes a back seat a lot as I am busy ensuring my family are cared for properly. It has been a real struggle to stay focused on diet since having both my children and there is very little support out there.

The diet is stressful and time consuming and with two children to raise, a full-time job and normal life stresses I just can't manage it successfully no matter how hard I try.

3.4. Support and information needs

Women described how they needed more psychology support to help them deal with their anxiety about pregnancy and counselling for their difficulties in forming intimate sexual relationships. They were upset that some GPs, gynaecology and obstetric support teams appeared to have limited knowledge about maternal PKU and that provided extra barriers to successful maternal PKU care. They also described conflicting or lack of information regarding breast feeding and the nutritional requirements of the mother with PKU.

Overall, 54% ($n = 143/263$) of women with PKU said the UK NHS should do more to help woman have a safe pregnancy with more support centred around their needs.

Verbatim extracts from women's responses about support needs

Maternal PKU is hard. It is a constant struggle to keep levels down and a constant worry that your baby will be healthy. Many health care professionals whom you encounter during pregnancy are not well enough educated on issues surrounding maternal PKU.

Most hospitals do not have much knowledge of PKU, so my local gynae team would question things that would worry me on occasion (i.e. risk of PKU being passed on to my baby), when logically I already knew of this through my Dietetic Team.

There should be more advice out there for women with PKU. No one understands, not the consultant led units in the maternity units, not the GPs and no working places are made aware.

4. Discussion

In maternal PKU, undoubtedly pregnancy is medically problematic, with all pregnant women considered at risk. The health professional focus is for the wellbeing of the foetus, with priority given to ensuring that women achieve satisfactory blood Phe control with appropriate dietary and medical support. Pregnancy should be associated with

positive emotions, but the results of our survey indicated that maternal PKU was a source of psychological morbidity for some women; raising feelings of negativity, ambivalence, distress, and, in some cases, even alarm.

Perception of pregnancy risk in maternal PKU affected women's behaviours and decision making. From the thematic analysis, they described their vulnerability and expressed worry and uncertainty about the outcome of pregnancies. They had anxieties about sex, struggled with religious or moral beliefs about contraception and felt a 'lack of control over their fate' during pregnancy. Some women did not perceive dietary treatment to be manageable. Some were so scared of becoming pregnant that they avoided sexual intimacy. When women were pregnant without having followed a pre-conception diet, they expressed feelings of guilt, shock, and were often overwhelmed. Others who experienced pregnancy, described a heightened sense of anxiety, worrying about every blood Phe result that was above or below the blood Phe target range or were disturbed by any delay in blood Phe results. This extra anxiety is concerning, as higher anxiety levels during pregnancy have been associated with spontaneous abortions [17], preterm births [18] and a higher level of postpartum depression [19].

Limited privacy in PKU clinics and lack of psychology support may hinder patients from discussing sexual issues during their routine clinic visit, prior to pregnancy. Women with PKU need to feel comfortable about discussing pregnancy and contraception issues with their medical teams and they commonly need reassurance about the choices that they make. It is essential that they receive compassionate, sensitive health care to discuss sexual health concerns. If support is received from their community GP services, it is crucial they are fully briefed about the risks of maternal PKU care. Genetic counselling is also recommended for all reproductive-aged women with PKU and should include information on reproductive choices and family planning.

Another issue for some women with PKU was the lack of privacy when they decide to consider pregnancy. They effectively must make their decision public through contact with the PKU clinic and implement immediate changes to their diets which are obvious to those around them within the workplace. This "public declaration" of their intention to have a child is considered intrusive and stressful by some women, who may otherwise wish to keep this confidential and it may even result in their reluctance to initiate the diet prior to conception.

Many women described their difficult battles with dietary management throughout pregnancy and the practical issues they encountered in implementing the strict PKU diet, although most women said they maintained blood Phe levels within target range during pregnancy. Some had inadequate and only intermittent access to low protein foods and protein substitutes, particularly when trying to adhere to the strict diet in the pre-conception period. Some women found the protein substitutes unpalatable, especially when they had pregnancy-related nausea and vomiting. Others struggled with calculating Phe exchanges, eating adequate calories to prevent catabolism, limited food choices and the extra time demands of this intensive diet and the time required to attend frequent medical appointments. This interfered with a woman's job and reduced her time available for paid work. It was apparent that strong social support from a partner and family was a critical factor in successful dietary management.

It was clear that many women stopped dietary management shortly after child birth. They could not cope with the pressures of strict dietary management and caring for their baby. Many described anxiety, depression, tiredness and inability to focus well after the birth of the baby and some described how they struggled with day to day child care. Postpartum depression in the general population is known to adversely affect infant caregiving activities such as breast feeding and sleep routines [20] and although it is not clear if the rate of postnatal depression is higher in maternal PKU, there remains a possibility that this may be exacerbated by higher blood Phe concentrations. It has been shown that women who remain on dietary care post pregnancy are likely to have fewer mental health issues and are better able to cope

with parenting [21] which in turn, has an important impact on the cognitive outcome of their children. Furthermore, women needed guidance about their own nutritional needs during breastfeeding whilst on the PKU diet post birth. This education should be given as part of antenatal care and women need practical support during breast-feeding.

None of the women said that they had been offered the drug sapropterin which may help ease the pressures of dietary management and improve blood Phe control during pregnancy, even though in England, the NHS commission sapropterin for maternal PKU care. Data suggests from case studies that sapropterin is safe in pregnancy and will lower blood Phe concentrations in sapropterin responsive women [22]. The women in this survey found a strict low Phe diet particularly difficult in the pre-conception period, and prescription of sapropterin to responsive women may lessen the time required to achieve acceptable blood Phe control prior to pregnancy. In addition, administration of sapropterin in combination with dietary treatment in the post-natal period may help women maintain blood Phe control within acceptable limits, assist women to sustain breast feeding by helping them eat sufficient calories, and lessen any PKU related symptoms due to poor metabolic control.

4.1. Limitations

We did not collect any control data about female reproductive health in the general population. We also did not collect data about the reproductive health of women under 18. Our sample of women was self-selected rather than by random, and it is unknown to what extent the sample matches the characteristics of the general population. Whilst it can be argued that only respondents with negative experiences of PKU responded to this questionnaire, as many as 300 women aged 18 years and over responded, so it is likely this is a good representation of views. Also, the questionnaire was completed independently of health professionals, so it was easier for women to express their 'true' opinion.

5. Conclusions

In conclusion, this survey reports the reproductive health experiences of 300 women aged 18 years and over with PKU. The results indicate that pregnancy fears are prominent from adolescence and for some women overarching concerns over their ability to cope with pregnancy led to a decision not to have children. Healthcare providers should be sensitive to the distress and anxiety experienced by many women and they should be offered psychology and other counselling to discuss their anxieties and sexual health. Although health care professionals are very attentive with dietary care in the pre-conception and pregnancy period, it is important that a high level of care continues postnatally. At this time, women need more practical and emotional support, so they are not left isolated to cope with parenting and their dietary treatment. It is important that non-dietary treatments, when appropriate, are offered to ease the burden of managing maternal PKU and that these are included in the pre-conception and post-natal care package.

Conflicts of interest

Suzanne Ford has received either funding to attend conferences or honoraria from Nutricia, Vitaflo International, Biomarin, and Mevalia. She is a member of a Nutricia Advisory Board on PKU.

Mike O'Driscoll has no conflicts of interest.

Anita MacDonald has received research funding and/or honoraria from Nutricia, Vitaflo International, Biomarin, Galen Pharmaceuticals and Mevalia. She is a member of the European Nutrition Expert Panel (Biomarin), member of Sapropterin Advisory Board (Biomarin), member of the Advisory Board entitled ELEMENT (Danone-Nutricia), and member of an Advisory Board for Arla and Applied Pharma

Research.

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