

## ORIGINAL RESEARCH ARTICLE

# The importance of information and support following a suspected second-trimester anomaly that is later discarded: A qualitative study of women's experiences

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## Abstract

**Introduction:** A second-trimester anatomy scan may identify a suspected minor fetal anomaly and/or “soft marker,” such as choroid plexus cysts or femoral shortening. Such findings can raise a medical concern, as they could indicate severe fetal disease; however, they are also often transient or a “false alarm.” The aim of this study was to explore the experiences of pregnant women, where a medical concern was raised at the second-trimester ultrasound scan and later discarded after follow-up examinations and diagnostic testing.

**Material and methods:** This study consists of qualitative, in-depth interviews with nine women, where a minor anomaly/soft marker was identified at the second-trimester scan and a severe anomaly was later ruled out. Data were analyzed using thematic analysis.

**Results:** The main source of worry was uncertainty about the possible implications for the pregnancy and the baby, particularly concerns about potential termination of pregnancy for a severe fetal condition. The women described four strategies to manage worry and uncertainty during the diagnostic process: (a) seeking additional information to feel more in control, and (b) using social networks to share their concerns. Some women tried to (c) mentally distance themselves from the pregnancy during the diagnostic period, while (d) extra scans could relieve worry and support attachment. The women appreciated when the fetal medicine specialist pointed to normal features in the pregnancy and the baby, as this provided some counterbalance to the sense of uncertainty. In general, the women expressed satisfaction with the information received during the diagnostic process. However, all of them were worried during the diagnostic process, and where this process was prolonged, such worry lingered even after the minor anomaly/soft marker had been discarded.

**Conclusions:** Diagnostic uncertainty cannot be avoided in obstetric ultrasound and the women concerned appreciated being informed about the suspected findings even if it caused increased worry. Expedient diagnostic processes may alleviate worry, but are not always possible. Women in a prolonged diagnostic process may benefit from

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psychological and social support in parallel with, and even beyond, the obstetric investigation. However, further research is warranted.

#### KEYWORDS

pregnancy, prenatal care, qualitative research, ultrasound, uncertainty

## 1 | INTRODUCTION

The second-trimester ultrasound examination allows for prenatal detection of severe and lethal fetal anomalies. Such information is valuable to prospective parents, as it allows for personal and clinical preparation for the birth of a special needs child or for the parental decision to terminate the pregnancy.<sup>1</sup> However, the second-trimester ultrasound may also reveal suspected minor fetal anomalies and/or “soft markers,” such as choroid plexus cysts, echogenic bowel, pyelectasis, or femoral shortening.<sup>2</sup> Such a finding raises a medical concern, as it could indicate more severe syndromes and diseases. However, it could also be transient and simply disappear as the fetus grows, or it could be a “false alarm” due to less-than-optimal scanning conditions or imaging quality. Often, such a medical concern can be discarded after follow-up ultrasound examinations, expert evaluation, and/or diagnostic testing.

The continued development and extended use of obstetric ultrasound technology allows for increasingly detailed assessments of the fetus and, consequently, there is a risk of more frequent identification of suspicious findings. As such, identifying and discarding ultrasound findings are common features of everyday clinical practice in fetal medicine. For prospective parents, however, a raised medical concern about a suspected finding (however minor it may be) is often an unexpected and unprecedented experience that causes significant worry and concern.<sup>3</sup> For the clinician, it can be challenging to counsel about suspected findings, particularly if the prospective parents are in emotional distress.<sup>4,5</sup> Furthermore, the waiting time for follow-up tests and examinations may augment parental uncertainty and worry,<sup>6,7</sup> and for some parents this worry continues to linger even after the medical concern has been discarded.<sup>8,9</sup> The importance of pre-test information and counseling is often stressed, but there has been less focus on the clinician's role in prospective parents' management of the diagnostic process and a “false-positive” result. In order to minimize potential psychological impact and offer appropriate care, more knowledge is needed on the prospective parents' experiences, thoughts, and concerns during and after the diagnostic process. The aim of this study was therefore to explore pregnant women's experiences of a second-trimester identification of a minor anomaly/soft marker that was later discarded.

## 2 | MATERIAL AND METHODS

An explorative research design<sup>10</sup> with qualitative interviews<sup>11</sup> was used to answer the research question in this study.

### Key Message

The suspicion of a second-trimester minor anomaly or soft marker causes worry in pregnant women. Early dismissal of such suspicion is preferable, but not always possible. A prolonged diagnostic process may cause continued worry even after the suspicion is discarded.

### 2.1 | Setting

In Denmark, antenatal care is offered for free to all pregnant women. Standard care includes a first-trimester scan with a combined risk assessment for aneuploidy at 11–14 gestational weeks, and a second-trimester fetal anatomy scan at 19–21 gestational weeks.<sup>12,13</sup> At Aarhus University Hospital, where this study was conducted, more than 5000 first- and second-trimester ultrasound scans are performed every year.<sup>14</sup> The hospital holds a tertiary center for fetal medicine and serves both women from the Aarhus catchment area and women referred from regional hospitals for expert evaluation. Routine first- and second-trimester scans in low-risk pregnancies are performed by certified sonographers. In the case of a detected or suspected minor anomaly/soft marker, the woman is referred to a fetal medicine specialist for further examination. If a minor anomaly/soft marker is confirmed, the woman will receive information and counseling. Relevant examinations, such as invasive or non-invasive genetic testing, MRI, and follow-up scans, will be offered.<sup>14</sup> In many instances, the medical concern can be discarded after a single follow-up expert scan, but it could also be that various diagnostic tests and several follow-up scans are necessary before the medical concern can finally be discarded.

### 2.2 | Study participants

Between September 2019 and December 2019, eligible participants were recruited by fetal medicine specialists and sonographers from the Fetal Medical Unit, Aarhus University Hospital. Purposive sampling was used to recruit pregnant women, where a suspected minor anomaly or soft marker was identified at the second-trimester scan, and where the medical concern was later discarded. Sample variation was sought for age, parity, and length of diagnostic process. The staff provided oral and written information about the aim and methods of the study and upon consent, the contact information

was forwarded to the first author (LT). After 14 women consented to being contacted for a potential interview, recruitment ceased. In February 2020, after all the women had given birth, they were contacted by LT, who at that time was a public health master's student. LT provided additional information about the study and answered any questions. Five women could not be reached by phone or text, but the remaining nine women agreed to participate in an interview. Participant characteristics are presented in Table 1.

## 2.3 | Data collection

Between February 2020 and April 2020, nine interviews were conducted at a time and place of the participants' choice. Two individual interviews were conducted at the participants' homes; however, as a result of the COVID-19 pandemic, seven interviews were conducted by phone. Information about the study was repeated before all interviews and informed written or verbal consent was obtained. It was clearly stated that participation was voluntary, and that consent could be withdrawn at any time during the research process. The interviews were informed by a semi-structured interview guide that was developed by the research group and based on the international literature and on the interdisciplinary clinical and research experience of the authors (for topics and examples of questions see Table S1). After pilot testing of the guide on two participants recruited through social networks, the interviews were performed by

TABLE 1 Participant characteristics (N = 9)

Characteristics	
Age <sup>a</sup> (years), mean (range)	29 (24–39)
Educational level <sup>b</sup>	
Low	1
Medium	2
High	6
Children <sup>a</sup>	
1	6
2	2
3	1
Ethnicity	
Danish	9
Other	0
Length of the diagnostic process	
<1 week	4
1–6 weeks	2
>6 weeks	3
Duration of interview	
Minutes, mean (range)	42 (24–69)

<sup>a</sup>At time of interview.

<sup>b</sup>Educational level is grouped in the categories low (1–10 years), medium (11–14 years), and high (>15 years).

LT under supervision of the last author (see Table S2 for Reflexivity). All interviews were digitally recorded, transcribed verbatim, and anonymized. Before data analysis, all transcriptions were read by SL and LT to assess the information power of the data material.<sup>15</sup> Owing to the detail and richness of the interviews, the data material was assessed to be adequate and sufficiently cohesive to provide for a credible analysis.

## 2.4 | Data analysis

Thematic analysis was used to identify patterns in the data.<sup>16,17</sup> Upon a thorough reading and open coding of all transcripts, SL and LT generated a list of potential, inductive codes, which was discussed with the co-authors. Subsequently, the list was reduced to a final coding structure. All material was then systematically coded by LT using NVivo 12 software (QSR International Pty Ltd., 2020). The content of all codes was read and summarized by SL and LT, and the relations between the codes and the full data set were critically discussed by all authors. The data were explored for “negative cases” and contradictory evidence in order to test the credibility of the themes. The analysis resulted in a total of four main themes, each with two to four subthemes, as illustrated by the thematic map (see Figure S1). In order to enhance the trustworthiness of the study, the results were then presented to and discussed with a group of interested fetal medicine specialists ( $n = 2$ ) and sonographers ( $n = 8$ ) in the fetal medicine unit. This involvement did not impact the result of the analysis, but gave important input for the discussion and implications for practice.

## 2.5 | Ethical approval

The study was approved by the Danish Data Protection Agency (J. No. 1-16-02-72-20) on February 13th, 2019. Informed consent was obtained from all participating women.

## 3 | RESULTS

The medical concerns in the nine individual cases are presented in Table 2. For four women, only a single extra scan was necessary to discard the medical concern. For the remaining five women, the minor anomaly/soft marker led to a diagnostic process with invasive tests and additional scans before the medical concern was discarded.

### 3.1 | Uncertainty about the potential implications

This theme consists of two subthemes: “Termination of pregnancy?” and “The dreaded mini-birth”.

When informed about the medical concern, all women reported feeling worried and sad. The main source of worry was

TABLE 2 Medical concerns in included cases

Case	Medical concerns
1	Short humerus
2	Short femur
3	Small head circumference
4	Unilateral choroid plexus cyst, echogenic focus in the heart, echogenic bowel
5	Small head circumference
6	Unilateral pyelectasis, fetal arrhythmia: ectopic beats
7	Small intracardiac mass, suspicion of rhabdomyoma
8	Persistent right umbilical vein
9	Bilateral hydronephrosis, single umbilical artery

uncertainty about potential implications for the pregnancy and the baby. All women, irrespective of the finding, worried whether such finding could be so severe that it would make them consider termination of the pregnancy (Table 3, quote 1). Thoughts about termination were described as particularly troublesome and worrisome because of the perceived late gestational age and the prospects of having to go through a “mini-birth” (Table 3, quote 2). Hence, the majority of women described the period between the medical concern and the discard as “hell” due the uncertainty of the situation and the sense of helplessness (Table 3, quote 3). This was particularly pervasive for the women who went through a prolonged diagnostic process.

### 3.2 | Managing the uncertain diagnostic process

This theme consists of four subthemes: “Seeking information and personal accounts,” “Social network is helpful—and a burden,” “Attempts of detachment,” and “Scans are helpful.”

The analysis identified a range of strategies employed to manage worry and uncertainty during the diagnostic process. The four main strategies are presented below.

Seven of the women reported a need for more knowledge regarding the suspected finding than they had received at the hospital, and many turned to the internet. In cases where the women had a particular finding to search for (eg, short femur), they sought this additional information to understand the potential severity of the finding and to feel more in control. In general, the women requested high-quality information, for example, from guidelines and official websites. More random internet searches often proved inappropriate, as the women were confronted with worst-case scenarios, causing worry more than providing helpful information. However, many women appreciated reading about pregnant couples in similar situations, as these stories gave them hopes of a happy ending. Interestingly, two of the women did not search for additional information because they were unsure of what to search for. The vague nature of the suspected finding and/or lack of information at the ultrasound scan meant that these women felt unable to search for precise and relevant information (Table 3, quote 4).

During the diagnostic process, seven women sought support within their social networks. They reported feeling comforted by sharing their worry, but also felt burdened by having to deal with the questions and concerns of others (Table 3, quote 5). A common feeling was that it was difficult for others to truly understand such an unusual and devastating situation, and friends who had been through something similar were held in high regard. The difficulty of the situation meant that two women chose not to tell anyone about the minor anomaly/soft marker, and, as a result, they temporarily withdrew from social relations. In addition, these women pointed out that a decision to continue or terminate pregnancy was a private matter between the couple and hence a reason not to involve their social network in the situation (Table 3, quote 6).

Following the medical concern, six women reported how they decided to mentally put the pregnancy “on hold” and tried to distance themselves from the baby in order to better cope with a potential termination (Table 3, quote 7). However, this detachment practice was reported to be increasingly difficult as the pregnancy proceeded (Table 3, quote 8). In particular, feeling the fetal movements or knowing the sex of the fetus made it difficult to establish and maintain a mental distancing. Also, for three women, the risk of termination induced a stronger attachment, as they felt protective toward their baby (Table 3, quote 9).

Six of the interviewed women used extra scans, in private and/or public sector, as a coping strategy both during the diagnostic process and after the medical concern was discarded. The women concordantly reported that extra scans could alleviate worry by providing evidence of and confidence that the baby was well and developing normally. Moreover, the scans were a source for bonding with the baby and reestablished feelings of joy and excitement about the pregnancy (Table 3, quote 10). However, the scans could also be a source of worry, which is described in more detail below.

### 3.3 | Worry after the medical concern was discarded

This theme consists of two subthemes: “No residual worry” and “Lingering worry.”

All women reported worry and uncertainty during the diagnostic process. After the medical concern was discarded, four women reported no residual worry, but for five women the worry continued to linger throughout the pregnancy.

For the four women who reported no residual worry, the medical concern was discarded after a single follow-up scan at the university hospital. Though waiting time for the follow-up scan was “hard,” it was also experienced as short (<7 days). In their own explanation, the short time between the medical concern and follow up, as well as a very conclusive discarding of the medical concern by the fetal medicine specialist, effectively relieved these women of their worry (Table 3, quote 11). This did not, however, equal a worry-free pregnancy, only that other concerns took over (Table 3, quote 12).

TABLE 3 Illustrative quotes representative of themes

Themes	
#	Quotes (pseudonym, length of the diagnostic process)
Theme 1: Uncertainty about the potential implications	
1	"We knew that if it was Down syndrome, then we would terminate the pregnancy. That's what made it so hard. We talked about if we should give him a name before a potential termination, and if we should have a funeral. It was absolutely awful." (Beatrice, >6 weeks).
2	"I was really worried about having to go through a 'mini-birth' to terminate the pregnancy if anything was wrong. That was almost the worst thing." (Anna, >6 weeks).
3	"The worst part is the uncertainty. Not knowing exactly what is wrong or how it might turn out." (Eloise, 1–6 weeks).
Theme 2: Managing the uncertain diagnostic process	
4	"I didn't go online in search of information because I didn't know what to search for." (Grace, <1 week).
5	"At first, it was nice to tell people what we were going through, and feeling that we were not alone. But later it actually became a little stressful that so many people around us were worried and sad on our behalf." (Diana, >6 weeks).
6	"I think we needed just to be alone as a couple. It was important to us that we were the only ones to decide what was going to happen." (Anna, >6 weeks).
7	"To some degree, I guess I distanced myself from the pregnancy. We did not talk about names or things to buy or stuff like that. We didn't want to get too attached to the child in case something was wrong." (Clara, 1–6 weeks).
8	"I tried to distance myself, but it was much harder in week 20 than in week 12." (Eloise, 1–6 weeks).
9	"I felt even more connected to him during that period. I think I was preparing for possibly having to say goodbye to him." (Beatrice, >6 weeks).
10	"That distance almost vanished when they confirmed that nothing was wrong. It put an end to those awful worries and the distance that I had created. We could go back to enjoying the pregnancy." (Eloise, 1–6 weeks).
Theme 3: Worry after the medical concern was discarded	
11	"The time between the two scans was horrible, but after that last scan we felt relieved and convinced that this was a suspicion that they deal with regularly and that everything was normal. So that was nice." (Harriet, <1 week).
12	"I was diagnosed with gestational diabetes a month later, so that kind of overshadowed everything else. In the last part of the pregnancy, we did not even think about those abnormal findings." (Clara, 1–6 weeks).
13	"I definitely did not trust that everything was okay. I was worried until the day I gave birth. I didn't trust that everything was normal until I finally had him on my chest." (Beatrice, >6 weeks).
14	"I was often scanned on Thursdays, and then Friday, Saturday and Sunday went just fine. But Monday, Tuesday and Wednesday I'd just got more and more nervous, worried and in a bad mood. And on those Wednesday nights I couldn't sleep. For weeks. It was incredibly tough." (Anna, >6 weeks).
15	"No doubt it will affect me, if we have another child. And I must admit that the desire to have more children after this pregnancy is basically non-existent ... because of the things I went through in this pregnancy." (Beatrice, >6 weeks).
Theme 4: Communication with healthcare providers	
16	"I would have liked some information about risk, etc. Some statistics on how many cases turned out to be normal. I like to have some numbers, so there could have been more of that." (Diana, >6 weeks).
17	"Of course, I would have liked to be without the worry. That being said, if they see something potentially worrying about my baby, then, of course, I would like to know. Otherwise, I would feel they kept something important hidden from me." (Grace, <1 week).
18	"They did an excellent job of explaining—and even drawing pictures—at the follow-up scan. So there were no lingering doubts ... and they really made an effort to make sure that we felt a sense of joy and relief." (Fiona, <1 week).
19	"After the scan, we felt calm ... because they really emphasized that we shouldn't worry. And we took that feeling home with us." (Harriet, <1 week).

Five women reported continued worry about the baby's health. Common to them was that the diagnostic process was experienced as long (between 2 and 16 weeks). They all reported that the worry lasted throughout the pregnancy and was not relieved until the birth of a healthy baby (Table 3, quote 13). As a result of the stressful situation, three women took sick leave from work for the remainder of the pregnancy. As mentioned above, extra scans

could provide some peace of mind, but also additional worry, as the women had now become aware that ultrasound can result in unforeseen findings and bad news (Table 3, quote 14). As a result, two women were very hesitant toward having scans in a future pregnancy and even toward getting pregnant at all, as their experience of the diagnostic process had been extremely uncertain and difficult (Table 3, quote 15). Despite their worry, the women

did not regret attending the second-trimester malformation scan or the extra scans.

### 3.4 | Communication with healthcare providers

This theme consists of two subthemes: “Information needs” and “Counterbalance worry.”

In general, the women expressed satisfaction with the information received at the fetal medicine unit during the diagnostic process. Healthcare providers were described as professional and compassionate when informing the women about the medical concern and the options available.

Six women called for specific, numerical information about risks and statistics (Table 3, quote 16) and those who received it appreciated the honest and straightforward communication from healthcare providers. All women agreed that if the fetal medicine specialist suspected any anomalies or soft markers, they wanted to be informed (Table 3, quote 17). Likewise, it was important that the health providers took the time to inform them about the medical concern and to answer potential questions (Table 3, quote 18).

All women appreciated that the fetal medicine specialist emphasized that the medical concern was “only” a suspicion, and that follow-up tests and scans could very well disconfirm the suspicious finding (Table 3, quote 19). Also, they appreciated being reminded that invasive procedures and follow-up scans are everyday procedures that many pregnant women go through. Finally, all women appreciated that the fetal medicine specialist also pointed to normal features in the fetus and the pregnancy, as this provided some counterbalance to the worry and feelings of uncertainty.

## 4 | DISCUSSION

The present study investigated women's experiences following the identification or suspicion of a minor anomaly or soft marker in the second trimester, where this medical concern was later discarded. This study provides a “patient perspective” on a common but complicated clinical situation and as such the results may contribute to improved clinical management and support for prospective parents. We found that the main source of worry was uncertainty about the potential implications for the pregnancy and the baby. The women employed a range of strategies to manage worry and uncertainty, such as seeking information to feel more in control and using social networks to share their concerns. Some women tried to mentally distance themselves from the pregnancy but found it difficult because of fetal movements and knowing the sex of the baby. Extra scans were reported to relieve worry and to support attachment for most women. In general, the women expressed satisfaction with the information received during the diagnostic process. However, all of them were worried during the diagnostic process and our results indicate that a longer diagnostic process

may cause worry to continue to linger even after the suspected finding has been discarded.

Our findings resonate with current research that indicates that women want maximum information about the fetus.<sup>18,19</sup> Similarly, the women in the present study agreed that they want the healthcare provider to share their suspicions and concerns even if such information is worrying. However, providing useful information can be difficult in these situations where the fetal medicine specialist cannot predict the significance of the finding or even if it can be considered abnormal.<sup>5</sup> The women in the present study called for more statistical and numerical information, but often that is not available. As a result, the uncertainty of the suspected finding is non-reducible and healthcare providers must embrace and acknowledge that this may cause worry and frustration in the pregnant woman/couple.

Furthermore, in cases of uncertain findings, healthcare providers must be very conscious about appropriate phrasing. Even so, miscommunication and misunderstanding may still occur. We were very surprised to find that the women felt immediate worry about possibly having to terminate the pregnancy. To the best of our knowledge, this is not a consideration that was presented to them by the healthcare providers. It is not customary or advised to address termination of pregnancy when counseling couples in this type of case and at this stage. However, to focus on the potential worst-case scenario is not an uncommon response when something of value is at stake,<sup>20,21</sup> and perhaps healthcare providers should be careful to underscore that at this point in the diagnostic process, termination is still a very unlikely outcome.

Our findings align with larger studies showing a correlation between maternal anxiety and diagnostic ambiguity, where the uncertainty of a finding can generate more anxiety than the severity of the finding.<sup>5,22,23</sup> Other studies have found that worry can be persistent even after a chromosomal analysis has ruled out aberrations<sup>9</sup> and even up to 2 months postpartum,<sup>8</sup> which also resonates with the present findings where women who experienced longer periods of diagnostic uncertainty reported lingering worry throughout the pregnancy. Importantly, those who experienced a short diagnostic process and a quick dismissal of the diagnostic ambiguity did not report lingering worry, and this finding calls for further investigation.

A speedy diagnostic process cannot always be accomplished, as further investigations may require time for the fetus to develop. The present findings suggest that prospective parents who deal with prolonged diagnostic ambiguity may need more appropriate care than is currently offered at our fetal medicine unit. First of all, it might be useful to screen prospective parents undergoing diagnostic uncertainty—for example, through a self-reported measure or scale—to identify problematic worry and offer additional support.<sup>24</sup> Second, our results indicate that these women and partners may need psychological and social support in addition to the obstetric investigation. Currently, our fetal medicine unit does not offer such support, and as a result we tend to offer these couples extra scans to relieve worry; in everyday practice, these are referred to as “comfort scans.” Our results indicate that an extra scan can relieve worry, but for some it may also be a source of additional worry, for example, in the days leading up to

the scan. Therefore, it may be useful to discuss the pros and cons of extra scans to make sure that the care offered is in accordance with necessary medical clarification and the prospective parents' preferences. Furthermore, more knowledge is needed on alternative and supplementary ways of best supporting the parents. For example, future research could investigate different approaches to dealing with ultrasound-induced worry in pregnancy, for example, interventions focusing on meta-cognitive approaches, mindfulness, or different types of online support.

The strength of the present study is the explorative, qualitative approach whereby the participating women were encouraged to share their individual thoughts and experiences, which allowed for an in-depth understanding not restricted by predefined options of a questionnaire. The present study is relatively small, which is a limitation. However, in qualitative research there is no uniform standard for assessment of adequate sample size, but the concept of "information power"<sup>15</sup> advocates that the more information a sample holds relevant for the study, the lower the number of participants needed. However, a larger sample size could have provided insights into a broader range of experiences. We have aimed to enhance the credibility of the study by providing a detailed and transparent account of the research process as well as the methodological and analytical decisions made throughout the data collection and analysis. The interdisciplinary research team ensured researcher triangulation throughout the study, and we have aimed to be reflexive about potential researcher impact on the material, analysis and conclusions drawn. Another way of enhancing credibility is the use of member-checking and/or formal patient involvement in the research process. This was not used in the present study; however, following each interview, LT summarized her understanding of the interview and so gave the women an opportunity to disagree and/or provide further details. Additionally, initial findings would often be informally discussed by LT and participants after each interview as an opportunity to test and challenge preliminary understandings. Results from qualitative research are not generalizable in the quantitative sense, nor are they intended to be. However, a qualitative understanding of a specific local context may be useful in other contexts, and we invite readers to reflect on the potential applicability of our results and related discussion in contexts outside Denmark.

## 5 | CONCLUSION

Diagnostic uncertainty cannot be avoided in obstetric ultrasound, and the women appreciated being informed about the suspected findings, even if it caused increased worry. Expedient diagnostic processes may alleviate worry, but are not always possible, and clinicians may struggle with how to best support the parents. Our results indicate, that women in a prolonged diagnostic process may need psychological and social support in parallel with and even beyond the obstetric investigation. However, more research is needed on the most appropriate

timing, target group and intervention types as well as the actual effectiveness of different types of psychosocial support initiatives.

## CONFLICTS OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

The study was conceptualized by LH, PS, IV and SL. The data was collected by LH and data analysis was performed by LH and SL. All authors participated in the interpretation of the result. LH and SL wrote the first manuscript draft, which was revised by all authors.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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