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Trials

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Impact of perinatal environmental health education intervention on exposure to endocrine disruptors during pregnancy—PREVED study: study protocol for a randomized controlled trial

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Abstract

Background: The suspected or actual effects on health of endocrine-disrupting chemicals (EDC) and their ubiquitous presence in everyday life justify the implementation of health promotion interventions. These interventions should ideally be applied during critical windows like pregnancy. Perinatal environmental health education interventions may help to reduce EDC exposure during pregnancy.

Methods/design: PREVED (Pregnancy, PreVention, Endocrine Disruptors) is an open-label randomized controlled trial assessing the impact of environmental health education intervention on EDC exposure during pregnancy. Inclusion, consent, and randomization take place during the first trimester. The participants are randomly allocated into three groups: (i) control group (information leaflet on EDCs), (ii) intervention group in neutral location (information leaflet and workshops in a meeting room), and (iii) intervention group in contextualized location (information leaflet and workshops in a real apartment). Workshops are organized between the second and third trimesters of pregnancy. Main outcome is the percentage of participants who reported consuming manufactured/industrial food. Secondary outcomes are as follows: (i) psycho-social dimensions, (ii) EDC concentrations in urine, (iii) EDC concentration in colostrum, and (iv) percentage of participants who reported consuming paraben-free personal care products.

Discussion: PREVED is a ground-breaking intervention research project dedicated to perinatal environmental health education that aims to identify pollutant sources in daily life and to offer accessible and realistic alternative solutions, by promoting the sharing of know-how and experience in a positive and non-alarmist approach.

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Trial registration: ClinicalTrials.gov: NCT03233984 (current status: ongoing). Retrospectively registered on 31 July 2017 (https://clinicaltrials.gov/ct2/show/NCT03233984) because when the first participant was enrolled in this non-drug intervention, ClinicalTrials.gov was centered in therapeutic trials.
The World Health Organization Trial Registration Data Set is in Additional file 1.

Keywords: Endocrine disruptors, Maternal exposure, Pregnancy, Environmental health, Intervention research, Randomized controlled trial

Background

The in utero period is an important period that conditions health in adult life. Prenatal exposure can disturb fetal and neonatal development [1] and lead to numerous disorders [2–4]. These health consequences are especially underlined by FOAD- (Fetal Origins of Adult Disease) [5], DOHaD- (Developmental Origins of Health and Disease) theories [6, 7], which emphasize the importance of intrauterine environmental exposure in offspring health, and by POHaD-theory (Paternal Origins of Health and Disease), which underlines the role of paternal environment and exposure [8].

The concept of "exposome" initiated in the 2000s is along the same lines. Indeed, exposome includes lifetime exposures from periconceptional period until death [9]. Under this concept, exposures can be classified as [10, 11]:

- Internal exposure: combining all endogenous factors
- Specific external exposure: combining exogenous factors such as chemical contaminants, environmental pollutants and lifestyle factors
- General external exposure: taking into account a wider environment with social, economic, and psychological factors

Among these exposure factors, endocrine-disrupting chemicals (EDCs) are chemicals and environmental pollutants defined by the World Health Organization (WHO) as "exogenous substances or mixture that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)-populations" [12]. EDCs may be synthetic such as parabens (PB) and phthalates found in cosmetics, bisphenol A (BPA) found in plastics, or pesticides such as atrazine or trifluralin found in soil or food. They may also be natural such as hormones or phytoestrogens [13].

Their involvement is confirmed, or at least suspected, in the development of numerous diseases or disorders, especially on reproduction, hormone-dependent cancers [14, 15], and metabolic disorders [16]. This is typically the case of diethylstilbestrol, an estrogen medication which was prescribed for pregnant women in the 1940s [17]. Many decades later, prenatal exposure to diethylstilbestrol was recognized as the cause of many diseases for children exposed in utero, and even for grandchildren who had never been directly exposed [18–20]. In fact, exposure to several EDCs at specific developmental stages called "susceptibility" or "critical windows" such as prenatal and puberty periods causes more pronounced health effects [14, 21, 22].

In 2016, the European Commission made recommendations on prioritizing human epidemiology (follow-up cohorts…), knowledge about exposure (chemical markers, biomarkers…), and effects in wildlife [23], and in its strategic approach, issued in 2018, emphasis was put on prevention interventions, particularly in "critical windows" [24]. Thus, several steps were necessary to take into account EDC exposure [25].

Promotion health interventions should be carried out since the pre/periconceptional period [26], which comprises key moments of exposure sensitization and environmental health promotion [27, 28]. There are numerous recommendations and interventions aimed at improving maternal and infant health, for instance, on nutrition [29–31], iron supplementation [32], physical activity [33], hypertensive disorders [34], oral health [29], or on reduction of environmental tobacco smoke exposure [35, 36]. However, only a few of them concern EDC exposure [37–40].

To our knowledge, there exists no research study focused on perinatal exposure through the prism of environmental health education in France. Our hypothesis was that an extended perinatal environmental health education intervention conducted during pregnancy by promoting the sharing of know-how and experience in a positive and non-alarmist approach would contribute to the reduction of EDC exposure.

The PREVED (Pregnancy, PreVention, Endocrine Disruptors) study aimed to assess the impact of an environmental health education intervention on prenatal exposure to EDCs. The secondary objectives are to assess the impact of the intervention on psycho-social dimensions, EDC concentration in urine and colostrum, and on the choice of personal care products. The EDCs

studied are BPA, its chlorinated derivatives, and PB: methyl-, ethyl-, propyl-, and butyl-PB.

Methods

Study design

The PREVED study is an ongoing open-label, monocentric, randomized (1:1:1) controlled superiority trial, parallel-designed, three-armed with:

- A control group: group (1)
- An intervention group in neutral location: group (2)
- An intervention group in contextualized location: group (3)

Participants and interventions

The PREVED study is conducted in Poitiers (France). Recruitment was held from April 2017 to April 2019. The site of intervention is in an underprivileged and multicultural Poitiers neighborhood with strong associative potential (animation center, young workers' home and sports center), where women of low socioeconomic and educational status may be particularly exposed to EDCs [41].

According to the allocation group, workshops are performed in two different locations. Group 2's intervention is performed in a meeting room in the "Animation Centre of the neighborhood," which is a neutral location. Group 3's intervention is performed in "*Atelier du 19*," an apartment dedicated to health/environment education in everyday life [42].

Inclusion and exclusion criteria are detailed in Table 1.

PREVED study implementation was preceded by an essential step involving pregnant women and professionals. Qualitative and quantitative studies were carried out to describe pregnant women's knowledge, attitudes, and behaviors towards EDC exposure [43], to estimate their risk perception [44], and to determine environmental health knowledge, attitudes, and practices of prenatal healthcare providers [45]. These results facilitated the design of the intervention and the identification of the aims and outcomes of PREVED study.

Furthermore, the study was preceded by the creation of a "DisProSE Group" steering committee, a consortium of researchers, local actors, and decision-makers who co-built the intervention, initially developed by a mutual insurance company, according to PREVED's aims and to behavior change techniques (BCT) taxonomy [46].

After complete recruitment, we could analyze the intervention, which involved 12 of the 16 BCTs, in view of diversifying approaches (Table 2).

No concomitant intervention is prohibited. Women randomized in the control group are told that they are entitled to have the program after the end of the study (1 year after delivery).

The list of pregnant women is obtained through pregnancy declarations, which are centralized in rance by "*Protection Maternelle et Infantile*" (maternal and child protection) or PMI. The investigator sends to eligible women an informative postal mail with a prepaid envelope. Women who wished to participate in PREVED study confirmed their interest by phone or mail.

To improve enrolment, information leaflets are sent to general practitioners and midwives working in the enrolment area. To achieve representative and adequate enrolment, PMI's midwives were trained to present the PREVED study to pregnant women. Local actors in social centers and the associative sector also assisted in enrolment. The first participant was enrolled on 17 April 2017.

The intervention consisted of a sequence of three workshops held between the second and the third trimesters of pregnancy. It incorporated the results of a previous workshop [43] and aimed to identify pollutant sources in daily life and to offer accessible and pragmatic alternative solutions by promoting the sharing of know-how and experience in a positive and non-alarmist approach. Three themes are addressed (Table 3). Any

Table 1 Inclusion and exclusion criteria for the PREVED study

Inclusion criteria	Exclusion criteria
- Pregnant women with declared pregnancy - Speaking French - Being aged 18 years or more - Living in the French department of Vienne and at less than 30 min from Poitiers - Having the intention to give birth in the maternity of the University Hospital, of the clinic "Fief de Grimoire" in Poitiers or in the Hospital of Châtellerault - Having signed a consent form	- Pregnant women expecting twins or more - Having a complicated pregnancy - Not speaking French - Being under 18 years old or under legal protection despite being 18 or more - Being deprived of liberty by judicial or administrative decision - Undergoing psychiatric treatment - Not being affiliated to a social security system - Intending to move out during the next year - Having the intention to give birth in a maternity ward other than the department of Vienne - Being unable to express consent

Table 2 Behavior change techniques (BCT) used for the intervention of PREVED study

Grouping of BCT taxonomy	Chosen BCT in each BCT group	Example of an intervention
Goals and planning	Problem solving	- To identify behaviours that are easy to implement daily to reduce exposure to endocrine disruptors chemicals (EDC) (example: replace plastic with glass)
	Action planning	- To integrate the purchase of primary products into your personal planning and devote time to manufacturing cosmetics at home
Feedback and monitoring	Not applicable	- No feedback between the workshops/Only a series of workshops by participant
Social support	Not applicable	- Few attendants came to the workshops
Shaping knowledge	Training on how to perform the behavior	- To learn to read package labels - To learn to prepare cookies and cosmetics at home
	Behavioral experiments	- To appreciate the changes implemented daily to reduce their exposure to EDCs thanks to the three-time questionnaire which to compare her consumption before and after
Natural consequences	Information about health consequences	- To respond to participants' questions about the known effects of EDCs exposure during pregnancy
	Information about social and environmental consequences	- To present the consequences of behaviours aimed at reducing EDCs exposure on the environment (example: waste reduction through homemade products)
Comparison of behavior	Demonstration of the behavior	- To teach how to make one's own cosmetics
Associations	Prompts/clues	- To highlight leaflets and documentation at home
Repetition and substitution	Behavioral practice/rehearsal	- To integrate the manufacture of cosmetics into your schedule: the recipes offered were inexpensive and easy to integrate into a routine without constraints
	Behavior substitution	- To avoid heating food in plastic dishes with a microwave oven
	Habit formation	- To encourage participants to ventilate the house for 20 minutes/day
	Habit reversal	- To use glass jars and boxes to store food and meal leftovers, instead of plastic packaging
	Generalization of target behavior	- To teach how to make one's own cosmetics in order to be independent/repeat the manufacture at home
	Graded tasks	- "Change everything" is neither taught nor required to propose simple solutions to reduce exposure to EDC
Comparison of outcomes	Credible source	- To use of current data from literature
	Pros and cons	- To explain that using glass packaging instead of plastic is valuable but not without some constraints (heavier, risk of breaking)
	Comparative imagining of future outcomes	- To project yourself at home (eliminating / reducing EDCs sources) in particular to safe your health and your children health
Reward and threat	Material reward	- To bring home the products made during the workshops (floor cleaner, cookies, ...): quick practice and experimentation directly after the workshop - To reimburse the travel costs of participants (planned but not implemented)
Regulation	Conserving mental resources	- To recall the pleasure of consuming healthy products - To encourage the implementation of even small changes on a daily basis: Choose not-guilty and counterproductive words
Antecedents	Adding objects to the environment	- To bring home made products: reusable containers will remind the participants of the value of making their own products and encourage them to continue manufacturing
Identity	Framing/reframing	- To rely on a presentation of a positive vision of health - Do not focus on pathologies - To encourage exchanges: sharing of experiences and knowledge is complementary to the information given by the facilitators
	Incompatible beliefs	- To remember that a "Natural Product" is not necessarily a "Safe Product" or a "Healthy Product" - To explain that it is not necessary to go from "all industrial" to "all homemade": by reading the labels, it is possible to better choose products containing little or no EDCs (number of ingredients, absence of 'additives ...)
Scheduled consequences	Not applicable	
Self-belief	Verbal persuasion about capability	- To reassure participants: no guilty speech - To highlight simple and accessible solutions to limit EDCs exposure: positive

Table 2 Behavior change techniques (BCT) used for the intervention of PREVED study *(Continued)*

Grouping of BCT taxonomy	Chosen BCT in each BCT group	Example of an intervention
		reinforcement
	Focus on past success	- To encourage the sharing of experience and information between participants (example: multiparous participants can advise new parents on "tips and tricks")
Covert learning	Not applicable	

participant may at any time withdraw from this study and adherence participation is encouraged with adapted meeting.

The DisProSE group produced an information leaflet providing advice on ways of reducing EDC exposure in relation to the aforementioned themes. This leaflet was designed according to the principles of health literacy to be as accessible and comprehensible as possible [47]. All participants, including group 1, receive it during the first home visit. The only difference between group 2's workshops and group 3's workshops is the location of the intervention.

Fig 1. summarizes the conduct of PREVED study.

Main outcome

- Percentage of participants who reported consuming manufactured or industrial food determined through a sociodemographic and consumption questionnaire (Q1) developed by our research team [48] and administered at t0, t + 2 months and t + 14 months.

Secondary outcomes

- Mean score of psychosocial questionnaire (Q2) developed by our team, whose dimensions are presented in Table 4
- Urinary concentrations of: BPA, chlorinated derivatives of BPA, methyl-, ethyl-, propyl-, and butyl-PB
- Concentration in colostrum of: BPA, methyl-, ethyl-, propyl-, and butyl-PB
- Percentage of participants who reported consuming PB-free personal care products

The planning of the administration of questionnaires and the collection of samples is summarized in Fig 2.

Time schedule of enrolment, intervention, assessments, and visits are detailed in Table 5. They were carried out according to the SPIRIT Guideline (Additional file 2).

Sample size

According to the results of the EDDS (Endocrine Disruptors Deux-Sèvres) cohort study, 83% of French women consumed canned food [48]. Thus, we calculated the number of participants based on the primary outcome measure (consumption measure) using a two-sided paired sample t test with 0.05 level of significance two-way design and β = 0.20. Our hypothesis was that the contextualized intervention would decrease this percentage to 60%, representing a decrease of 23 points, and 58 participants were required for each group. We expected 20% of lost to follow-up participants; consequently, 70 participants are required for each group, out of a total of 210 pregnant women to be included in our study. This number was increased to 273 persons due to significant colostrum loss in an amendment submitted to the Committee for Personal Protection who approved the first protocol (protocol version 10 approved by the Committee for Personal Protection on 15 June 2018).

Assignment of interventions

The trial is open-labeled but a central random blind-generated allocation was performed before the first home

Table 3 Detailed workshops for the intervention of PREVED study

	Workshop 1	Workshop 2	Workshop 3
Theme	Indoor air quality	Nutrition	Personal care products
Duration	2 h	2 h	2 h
Participants	10 people: pregnant women ± spouse, friend, or parent	10 people: pregnant women ± spouse, friend, or parent	10 people: pregnant women ± spouse, friend, or parent
Facilitator	Medical advisor for indoor environments	Dietician trained in environmental health	Cosmetologist
Pedagogic objectives	- To detect and reduce sources of domestic air pollution - To share know-how, experiences, and information on alternatives	- To identify food pollutants - To share know-how, experiences, and information on alternatives	- To identify necessary elements to make healthy choices of personal care products and clothes - To share know-how, experiences, and information on alternatives

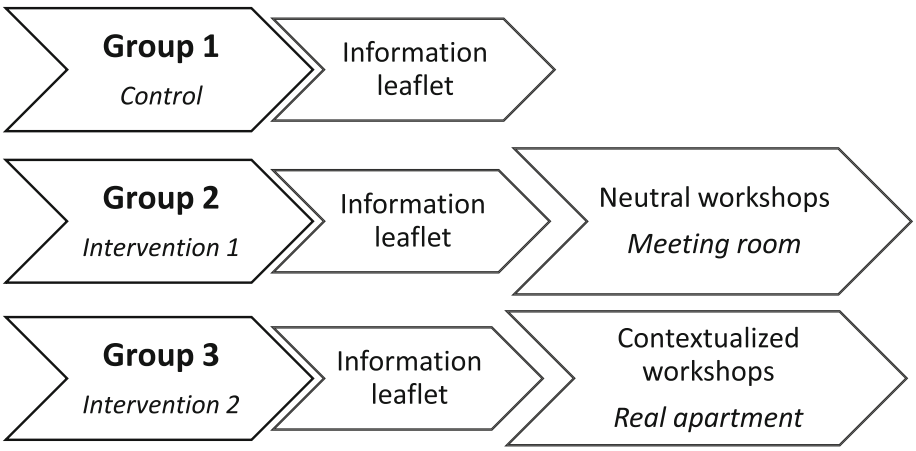

Fig. 1 Description of the three groups of the PREVED study

visit. The methodological referent of PREVED study enrolled the participants. A number was assigned to each participant. The random blind-generated allocation with 1:1:1 ratio is based on fixed blocks of 3 before the first home visit. The allocation sequence is generated on Microsoft EXCEL® (function RAND) by a doctoral student. Participants were then randomly assigned to one of the three groups by a research nurse who is also trained in indoor environments.

This type of study design did not allow a blinded trial as is the case in intervention research.

No changes were planned to randomly assigned groups.

Data collection, management, and analysis

The research nurse performs home visits and collected data at four key moments (Table 5):

Table 4 Dimensions of the psychosocial questionnaire used in PREVED study

Dimension of the psychosocial questionnaire	Origin of corresponding question or questions	Comment
Self-esteem	French version of the "Self-esteem scale" [49]	Score ranges from 10 to 40: the lower the score, the lower self-esteem. Items for this score are self-administered
Perceived health	Created for the questionnaire	Score ranges from 0 to 100 on a visual analogic scale
Health care renunciation and risk aversion	Inspired by French national investigations [50, 51]	Use of visual analogic scales
Risk perception	Created for the questionnaire and based on the Perception of Pregnancy Risk Questionnaire [52]	Use of visual analogic scales. A composite and global score of perinatal risk perception related to EDC exposure was created
Knowledge about endocrine-disrupting chemicals (EDCs): routes and sources of exposure, ability to name some EDC's molecules or families of molecules and definition of an EDC	Created for the questionnaire	A composite score was created. A catalog of photo images illustrates sources of exposure
Perceived knowledge about EDCs	Created for the questionnaire	Use of a visual analogic scale
Expectations for a "healthy baby"	Based on "the healthy baby concept" [53]	Use of a visual analogic scale and a catalog of photo images
Trusted person	Created for the questionnaire	The answer to this question aims to identify the trusted person, who exerts the most influence on the pregnant woman
Level of concern about five risks related to pregnancy	Created for the questionnaire	This exploration is meant to establish a hierarchy, with respect to chemical risk concerns. A catalog of photo images is used
The way the pregnant woman heard about EDCs and, if so, how she experienced the information she received	Created for the questionnaire	These two parameters explore the role of information provided by the media, professional studies, and relationships (personal, friendly, professional, health professionals)
Relationship to risk visibility	Created for the questionnaire	Likert-type response

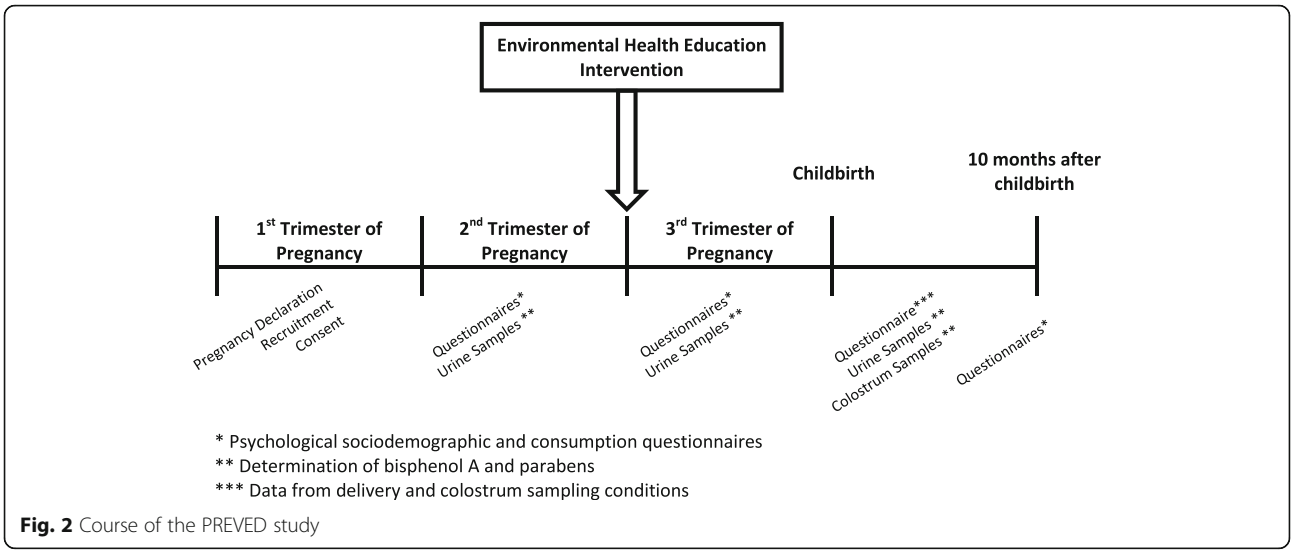

Fig. 2 Course of the PREVED study

- Home visit 1: Q1, Q2, and urine analysis
- Home visit 2: Q1, Q2, and urine analysis
- Childbirth: childbirth data, urine, and colostrum analysis
- Home visit 3: Q1 and Q2

Data input is entered by the research nurse and by the study site coordinator on electronic case report forms (e-CRF). Quality control and queries are carried out regularly. Telephone reminders are expected, if necessary, for home visits 2 and 3.

Urine and colostrum samples are collected in glassware provided by the investigator. They are stored at −80 °C, in polypropylene tubes, in the Biological Resource Centre of the University Hospital of Poitiers (no. BB-0033-00068) for 5 years. These samples are analyzed using reliable ultrasensitive methods previously developed by our research team for BPA and its chlorinated derivatives [54, 55] and new methods for PB developed

Table 5 SPIRIT flow diagram of schedule of enrolment, interventions, and assessments in PREVED study

	Enrolment	Post-allocation				Close-out
Timepoint	***Baseline***	t_0	t_{+1M}	t_{+2M}	t_{+4M}	t_{+14M}
		Home visit 1		Home visit 2	Childbirth	Home visit 3
		Leaflet	Workshops			
Enrolment:						
Eligibility screen	X					
Informed consent	X					
Allocation	X					
Interventions:						
Group 1 *Control group*		X				
Group 2 *Intervention group in neutral location*		X	X			
Group3 *Intervention group in contextualized location*		X	X			
ASSESSMENTS:						
Q1 *Sociodemographic questionnaire + consumption habits*		X		X		X
Q2 *Psychosocial questionnaire*		X		X		X
Collection of urine samples		X		X	X	X
Colostrum samples					X	

for this study. All laboratory materials and solvents are tested to ensure that they were free of contamination from target compounds. High-quality compounds and solvents are supplied by reagent manufacturers. Samples are prepared and extracted. Analyte concentrations are determined using Ultra Performance Liquid Chromatography (Shimadzu®, Kyoto, Japan) coupled to an API 6500+ mass spectrometer (ABSciex®, Concord, Canada) equipped with an electrospray ionization (ESI) interface, operating in negative ionization mode. Target analytes are analyzed in multiple-reaction monitoring (MRM) mode using two specific transitions per analyte to ensure the selectivity and the sensitivity of the method. The analytical methods used are validated according to international guidelines [56–59]. These methods allow to detect and quantify trace concentrations of unconjugated forms of BPA, its chlorinated derivatives, and PB. Urinary concentrations of analytes are corrected using urinary creatinine concentrations determined with a Cobas® 8000 (Roche Diagnostics, Mannheim, Germany) and using urinary specific gravity determined with a handheld refractometer.

Firstly, a descriptive analysis will be performed on sociodemographic data, questionnaire scores, and on EDC concentrations with percentage for qualitative variables and mean, standard deviation, median, maximum, and minimum for quantitative variables.

Baseline measurements of the three trial arms will be compared using paired t tests and χ^2 tests for the analysis of Q1 and EDC concentrations. The results of Q2 in the three groups will be compared by dimension using ANOVA analyses. An intention-to-treat analysis will carried out, and then a per-protocol analysis in aim to take into account population relating to protocol non-adherence.

Main outcome will be compared between home visit 1 and home visit 2. The rest of analysis will be performed between home visit 1, home visit 2, and home visit 3. Multivariate logistic regression will be performed to assess factors influencing main and secondary outcomes.

All statistical analyses will be performed using SAS 9.4® (SAS Institute, Cary, North Carolina, USA).

No interim analyses are scheduled.

Monitoring

A data monitoring committee was composed by a team from the Research Directorate of University Hospital of Poitiers. It is in charge of auditing trial conduct every 4 months, data management and promoting data quality. It consists of a Clinical Research Associate, a project monitoring manager, a data manager, and also the clinical trials vigilance unit. Consistency tests were performed on e-CRFs. As the study carries no risk, only consent and reporting of serious adverse events are verified.

The only expected adverse event was anxiety. Adverse events are noted at each home visit, throughout the period of participation of pregnant women.

Discussion

To our knowledge, PREVED is the first study to assess the impact of perinatal environmental health education by promoting the sharing of know-how and experience in a positive and non-alarmist approach. Along with the randomized controlled trial, a sociological approach is applied to analyze the conditions of reach, efficacy, adoption, implementation, and maintenance of the intervention [60]. In particular, observations are carried out during the workshops using grids and describing the interactions between the pregnant women and the workshop animator [61]. Moreover, interviews with stakeholders (researchers, local actors and decision-makers) are conducted to evaluate the transferability of the intervention [62]. The collective and local dynamics underlying the development of intervention and the points of view of participants are thereby assessed [61].

The PREVED study adopted two complementary approaches in the framework of the intervention research process. In fact, intervention research applied to the health field is a specific kind of research that aims to provide information on the impact of interventions on population health using scientific methods [63] and to determine how “to intervene” (not “to discover”) [64]. This design should be well-founded and include partnerships with practitioners [65]. Thus, DisProSE group facilitated partnership with different stakeholders through an interdisciplinary approach.

The PREVED intervention takes on the form of practical 2-h workshops. This configuration is easily reproducible and viable. Indeed, in addition to mention of the effectiveness of intervention research, degree of viability and specification of the mechanisms explaining the effects should be considered in conjunction with “the interventional system” [66].

Furthermore, the main feature of PREVED study is to consider all aspects of lifestyle and to underscore key functions such as sharing of know-how, sharing of experiences and information between participants. In fact, few environmental promotion interventions have shown that EDC exposure was reduced by changing lifestyle. However, previous studies assessed the impact by taking into account only one component of lifestyle, such as nutrition or cosmetics [67, 68] and did not include the dimension of “know-how” [69]. Moreover, these studies took EDC concentrations in urine as their main outcome, even though analysis of the latter may be unreliable [70–72] and did not provide information about

psychosocial aspects. This facet will be explored by the psychosocial questionnaire Q2 in our study. Concerning assessment of exposure to EDCs, we chose urine matrix samples because spot samples of urines are not restrictive and ensure optimal acceptability for the pregnant women participating. Twenty-four-hour urine collection may have been preferable, due to non-influence of the time of day. However, spot samples of urines provide reasonably reliable information on impregnation by BPA and PB during pregnancy [73–76].

We made sustained efforts to minimize information bias. Notwithstanding the absence of blindness, the investigator's practices and behaviors are likely to vary during visits, according to allocation group. That is why hetero administration of questionnaires by a single trained assessor, with a standardized interviewer's guide, has been adopted. Furthermore, selection bias is controlled by trained PMI nurses wishing to facilitate the enrolment of pregnant women facing difficulties. Enrolment bias is thereby avoided, whereas preceding studies highlighted the fact that participants for this type of study are mostly women with a high socio-economic level [48]. However, in such a cohort, selection bias can still be expected [77] especially for pregnancy cohorts, insofar as women with a high socio-educational level are likely to feel more concerned [78, 79]. We will probably need to determine how to reach populations more effectively in precarious situations. At the time of the analysis, results will be adjusted on confounding factors that affect the psycho-social dimensions and have been highlighted in this study.

Conclusion

Through this study, we aspire to increase all health stakeholders' awareness of the importance of primary prevention on exposome, especially EDC exposure, during pregnancy. In fact, given the methodological difficulties in proving EDC's effects in humans, some authors are convinced that it is impossible to conclusively demonstrate, and they would rather think in terms of prevention actions. That is why research studies should be complemented by interventions designed to reduce EDC exposure, such as primary prevention interventions, notably during pregnancy and other critical windows [28, 80, 81]. This approach also provides the scientific community and decision makers with elements possibly reinforcing their commitment to environmental health promotion.

Trial status

Since the last recruitment took place in the end of 2019, the last visit will be planned in the end of 2020.

The choice to publish the study protocol after recruitment completion but before the last visit can be justified by the particularity of population health intervention research.

In fact, this kind of study design integrated an "interventional system" as defined by Cambon L et al. as "a set of interrelated human and non-human contextual agents within spatial and temporal boundaries generating mechanistic configurations—mechanisms—which are prerequisites for change in health" [82]. Hence, this "interventional system" required continuous adjustment to the intervention context. That is why theorization of the methodology, and consequently of the protocol, requires more time than a classic therapeutic trial. As a result, we had to step back after the intervention and integrate the dynamism of the interventional system in order to improve the quality of our assessment.

Abbreviations

ANOVA: Analysis of variance; BCT: Behavior change techniques; BPA: Bisphenol A; DOHaD: Developmental Origins of Health and Disease; e-CRF: Electronic case report forms; EDC: Endocrine-disrupting chemical; EDDS: Endocrine Disruptors Deux-Sèvres; ESI: Electrospray ionization; FOAD: Fetal Origins of Adult Disease; MRM: Multiple-reaction monitoring; PB: Parabens; PMI: Protection Maternelle et Infantile; POHaD: Paternal Origins of Health and Disease; WHO: World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05813-5.

Additional file 1. World Health Organization - Trial Registration Data Set

Additional file 2. SPIRIT checklist PREVED Study

Additional file 3. Study Period

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Authors' contributions

This work is the result of numerous collaborations and exchanges. St.Ro., M.A.-L., V.M., Sy.Ra. designed the protocol. St.Ro., M.A.-L., V.M., Sy.Ra., H.E.-O, and DisProSE Group participated in design and validation of the intervention. A.-S.G. and F.P. recruited the women who participated in PREVED study. M.A-.L. and L.S.-R. supervised the human and social sciences approach. St.Ro. and M.A.-L. designed the questionnaires. St.Ro., A.D., and N.V. developed

analytical methods for determination of EDCs in urine and colostrum. A.-S.G. was the research nurse of PREVED study. G.C and P.P.E contributed to sample analysis. H.E.-O, St.Ro., and M.A.-L. wrote the paper. H.E.-O and St.Ro contributed equally to this work. All authors read and approved the final manuscript.

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Availability of data and materials
Paper questionnaires will be automatically anonymized to be entered on e-CRF anonymously and then stored in a locked cupboard. Biological samples will be identified only by the anonymity code.
The data sets generated and analyzed during this study are not publicly available. The methodological referent and the doctoral student will have access to the final trial dataset and results will be published in a peer-reviewed journal in 2021 with a defined authorship (Additional file 3). As of now, data have yet to be analyzed.

Declarations

Ethics approval and consent to participate
The PREVED study is sponsored by the University Hospital of Poitiers (Contact: Véronique FERRAND-RIGALLAUD). The methodological referent obtained informed consent signed by all participants. Pregnant women are free to leave the study at any time. Additional informed consent forms were developed for collection and use of additional data and biological specimens for two ancillary studies, which were also approved:

- PREVED microbiota
- PREVED placenta

This trial has been approved by Ethics Committee of the University Hospital of Poitiers, France: approval no. 2015-18 RR/MLB/LB and Committee for Personal Protection (CPP) – Ouest III: approval no. 2015-A00031-48 (HPS). It was registered on the Clinical Trials website, ClinicalTrials.gov (NCT03233984). Results will be published in a peer-reviewed journal. This protocol follows SPIRIT guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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