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Research

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Shared Decision-Making Regarding Place of Birth—Mission Impossible or Mission Accomplished?

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ABSTRACT

Aim: To explore Dutch pregnant women's experiences of shared-decision making about place of birth to better understand this process for midwifery care purposes.

Design: Qualitative exploratory study with a constant comparison/grounded theory design.

Methods: We performed semi-structured interviews, including two focus groups and eight individual interviews among 16 primiparous and multiparous women with uncomplicated pregnancies. Consent was obtained and interviews were audiotaped and fully transcribed. The interviews were analyzed utilizing a cyclical process of coding and categorizing, following which the themes were structured based on the three-step shared-decision making model of Elwyn.¹

Results: We identified the three themes according to Elwyn's model: Choice talk, Option talk and Decision talk. We expanded the model with one additional theme: Decision ownership. The four themes explained women's decision making process about place of birth. Women perceived shared-decision making about place of birth as a decision to be taken with their partner instead of with the midwife. Women and their partners regarded the decision about place of birth as a choice to be made as a couple and expecting parents; not as a decision in which the midwife needs to be actively involved. Women and their partners considered their options and developed a strong preference about where to give birth; even before the initial contact with the midwife was made. Involvement of the midwife occurred during the later stages of the decision-making process, where the women sought acknowledgement of their choice which was already made.

Conclusion: Women considered their partners as the most and actively involved in the shared-decision making process regarding the place of birth. The women's decision-making process about the place of birth did not fully occur during the antenatal care period. The midwife should ideally be involved before or during the early stages of pregnancy to facilitate the process.

KEY WORDS: Shared-decision making; Midwifery; Antenatal care; Pregnancy; Place of birth.

INTRODUCTION

Women in the Netherlands with uncomplicated pregnancies receive midwife-led care and can freely choose between birth at home, at a birth centre or at a short-stay hospital birthing unit. Midwife-led antenatal care commences at approximately seven weeks of gestation.² Midwife-led births are managed according to a physiological approach.² Within this physiological management of birth, midwives do not offer interventions such as medical pain relief, augmentation, or continuous fetal monitoring. If complications arise, interventions are needed, or when medical pain relief is requested or required, women are transferred to an obstetric-led unit.³ The Dutch maternity care system and management of midwife-led care, specifically homebirth, has received a lot of negative criticism.^{4,5} Safety of homebirth was widely and publicly debated. This negative publicity of homebirth has resulted in a decreased homebirth rate

in the Netherlands; a decline from 32% between 2001 and 2003 to 13% in 2015.⁶ Despite this debate and decline in homebirth, the Dutch homebirth number still represents one of the highest rates amongst the Western countries.⁷ In the Netherlands, an annual number of 66,790 pregnant women with uncomplicated pregnancies have to make a choice about the place of birth.⁶ A Dutch study, including a sample of 2,854 women receiving midwife-led care, showed that 49% nulliparous and 36.6% parous women preferred a short-stay hospital birth, 38.3% nulliparous and 53.3% parous women articulated a preference for a home birth; and 12.7% nulliparous and 8% parous women were undecided up to 35 weeks of gestation.⁸

In order to optimize Dutch maternity care services, recommendations have been drawn up in a governmental report.⁹ The first and main key point comprised: *Mother and the (unborn) child at the centre of midwifery care*,⁹ including offering choices and information, and addressing the woman's needs, preferences and choices regarding the place of birth.^{9,10} Midwives play an important role in offering women information and helping them to find, shift, and interpret information in order to make choices.¹¹ Given the importance of this finding, midwives need to consider their role in women's decision-making concerning the place of birth. There is ample evidence of the *why* factors that influence women's decision where to give birth, including the midwife's role,^{8,12-21} but we have little information and understanding about *how* women's decision-making process takes place determines the place of birth and *how* the midwife is involved in this process. When midwives understand the woman's decision making process regarding place of birth and how to support this process, they are better equipped to facilitate women's decision making in their care and it will allow midwives to move away from a 'home *versus* hospital birth' debate.²² In a maternity care system where home-birth is an integrated part of maternity services and where midwives are the main care providers during pregnancy; who aim to maintain the provision of offering homebirth to healthy women,^{2,10} it is important to fully understand the features of women's decision making about place of birth^{2,10} in order to facilitate this process.

In an earlier midwifery study,¹⁹ Elwyn's model of

shared-decision making was recommended as a potential valuable and practical model to support women's decision making processes about the place of birth. This model outlines a step-wise process for shared-decision making, (Table 1) where the emphasis is on the process of coming to a decision between woman and midwife.¹ The Dutch organization of midwives (KNOV) recommends the importance of shared-decision making in midwifery care, including place of birth.¹⁰ Following theoretical¹⁹ and practical¹⁰ recommendations, we have chosen Elwyn's model to underpin our study.

In this study, we aimed to explore and understand the process features^{25,26} of shared-decision making experiences about place of birth of pregnant women who receive midwife-led care in order to yield either a discussion or a propositional theory, building on Elwyn's theory of shared-decision making.¹ According to Elwyn's model, the midwife is the woman's designated partner in shared-decision making and thus the antenatal care period is the appointed period to apply the steps of the model. Because women with uncomplicated pregnancies can freely choose their place of birth, the Netherlands is one of the few countries in the Western world where such a study can be performed.

METHODS

Design

This qualitative exploratory study is based on a constant comparison/grounded theory design²⁵⁻²⁷ utilizing various methods for data collection, being focus groups and individual interviews.

Participants

We aimed to recruit pregnant women from various Dutch regions as the places of birth numbers (*i.e.*, *home*, *birth centre*, *hospital*) vary locally.²⁸ We included Dutch speaking pregnant women with uncomplicated pregnancies; with a gestational age of ≥ 27 weeks of a single child, and when at term presented by the vertex; anticipating the woman had received information about

Table 1: Three Step Shared-Decision Making Model.^{1,23,24}

Step 1. Choice talk

Introducing that a choice/ decision needs to be made. Making sure that the woman knows that options are available.

Step 2. Option talk

List/ describe options. Providing more detailed information about the woman's possible options and its consequences. Exploring the woman's knowledge, preferences, wishes, needs and values.

Step 3. Decision talk

Deliberation, supporting and considering the woman's preferences and deciding what is best. Making the final consensus-based decision.

labour and birth, including place of birth.² We excluded pregnant women with complicated pregnancies³ and those women with a priori determined intrapartum interventions requiring a planned (obstetric-led or shared care) hospital birth.³ We included 16 participants in our study, from different parts of the Netherlands (west, central and south). The mean gestational age was 32.3 (SD 3.49, range 27-38) weeks. All the participating women were living with their partner. Nine women were expecting their first child, four their second and three their third child. All but two women (Somalia, Morocco) had a Dutch ethnicity. Twelve women preferred a short-stay hospital birth and four women decided to have a homebirth.

PROCEDURE

To recruit eligible women for our study a purposive sampling was used, according to our preselected criteria. We decided on theoretical sampling, based on the cyclical nature of the data collection process²⁵⁻²⁷ and applied mixed recruiting strategies.²⁶ Between December 2014 and February 2015, we approached women *via* approximately 125 midwifery practices throughout the Netherlands (January to March 2015). To expand and refine the collected data already gathered,²⁶ we also approached women *via* antenatal education groups to recruit more participants (March 2015). Additionally, we approached pregnant women in person and through Facebook within our networks to recruit participants.

The researchers (AB, EOH, DdR) were final-year midwifery students. They had received training about interview techniques and had conducted a literature review about shared-decision making prior to the study. They reflected on their own ideas and thoughts about the concept. They regarded their own perceptions of shared-decision making as predominantly theoretical, which were not believed to influence participants' answers or cause researchers' bias.²⁶ None of the interviewers were personally or professionally related to the interviewees assuming the limitation to gratitude bias.²⁶

We conducted two focus groups interviews consisting of respectively five (3 March 2015) and three women (30 March 2015), and eight individual interviews (between 13 March to 2 April 2015). Due to illness, the second focus group was smaller than anticipated (n=5). Focus group interviews took place at midwifery practices at an agreed time suiting all participants. The individual interviews were conducted at a time and place convenient for the participants, which was either the midwifery practice or the woman's own home. Two women preferred a telephone interview.

Ethical Consideration

The Rotterdam Research Ethics Committee confirmed that because of the non-invasive character of the study ethical approval was not required, and we were advised to conform to the ethical principles of the Central Committee on Research

Involving Human Subject.²⁹ We obtained written consent from all the participants in our study. All participants received a written statement assuring anonymity and confidentiality and declaring that they could freely withdraw from the study at any time.

Data Collection

The participants were briefed about the purpose of the study. We emphasized that there were no wrong answers and participants were encouraged to reveal anything they wanted to say about the topics addressed during the interview, positively and negatively. The interviews were audiotaped and the consent for audiotaping was obtained prior to the interview. A semi-structured interview guide (topic list) was developed and used to maintain focus during the interviews. The topic list was structured according to the three steps of Elwyn's shared-decision making model (Table 2). Specific open-ended conversational-phrased questions were formulated to obtain some uniformity in how questions were asked in the different interviews. The first focus group and individual interview were regarded as pilot-interviews to increase reliability and internal consistency of the interviewers' usage of the topic list²⁷ and to check comprehensibility and clarity of the questions asked. We evaluated the pilot-interviews amongst the research team, with peer final-year midwifery students and midwifery tutors. One question was taken into account; no questions were added.

The interviews with the focus groups lasted between 45 to 60 minutes and the individual interviews between 25 to 30 minutes, excluding instruction, introduction and summary. Three researchers (AB, EOH, DdR) were present during both focus group interviews and two researchers alternately conducted the individual interviews. One researcher coordinated the interview and asked the questions and the other researcher(s) observed and noted non-verbal communication (field notes) of the interview and checked if all topics were addressed. To validate the findings, the researchers checked the interpretation of the answers from the participants by summarizing the answers, throughout and directly following the interview.²⁶ After each interview, the interviewers evaluated the findings and formulated topics that called for more in-depth exploration in the next interview, according to the cyclical process of the constant comparison design.^{26,27} One additional topic emerged during this process (Table 2). After each subsequent interview, the researchers reflected and explored their own thoughts about what was said during the interview, to minimize personal bias.²⁷

Data Analysis

The recorded interviews were transcribed verbatim and emailed to the participants for a member check, giving them an opportunity, should they wish, to change or remove any data.^{26,27,30} All participants agreed with the transcripts and no data were removed. We anonymized the transcripts. As a reliability check, we read the transcripts several times to get a sense of

Table 2: Topic List.		
Introduction		
Choice place of birth		
Timing 'birth talk'		
Experience/opinion 'birth talk'		
Topics according to SDM*-steps and procedural aspects		
Choice talk	Option talk	Decision talk
Being aware of options	Moment(s) of information	Decision support
Moment(s)/ timing introduction options	Methods of information	Voicing preference
Exploring own role	Content of information	Methods of enquiry preferences
Being aware of preferences	Available time information given	Moment(s) of enquiry preferences
	Tailoring information to wishes and needs	Midwife's response to preference
	Discussing pros & cons/harms and benefits	Coming to a final decision
	Deliberation	Voicing the final decision
	Involving others	Clarity decision
	Exploring preferences	Decision support
Process		
Expectations of contributing role midwife regarding decision making process/path		
Balance of decision between woman and midwife – 'who tipped the scale or was balance struck' (sense of autonomy)		
Decision made being based on informed choice		
Significance of decision		
Respect for decision		
Satisfaction with the decision and decision-making process/path		
Relation with midwife (e.g., trust)		
Positive aspects and aspects of improvement		
Added topic		
The woman's perception, meaning and interpretation of shared-decision making (as a concept)		
*SDM: Shared-decision making steps ¹		

the content as a whole.²⁷ Each interview was directly transcribed and coded after the interview had taken place. The field notes were added to the transcripts and used to aid the interpretation of the recorded data.^{26,27} The researchers categorized the data by connecting the codes. We shared and discussed findings and meaning throughout the data collection period.²⁵⁻²⁷ We reached theoretical saturation on all categories. Finally, the categories were reduced to core themes²⁷ using Elwyn's shared-decision making model as a framework in order to answer the research question as adequate as possible.²⁷ We added one separate theme in order to reflect the completeness of the data.²⁷ Examples of the analytical coding process are shown in Table 3.

RESULTS

We explored the shared-decision making experiences about place of birth of Dutch pregnant women who received midwife-led care. Our findings were structured in four main themes that reflect a comprehensive understanding of the features of this phenomenon.²⁷ The themes included: Choice talk, Option talk,

Decision talk, and Decision ownership. Quotes were added to illustrate the findings. The quotes were translated from Dutch to English by a native bilingual speaker.

Choice Talk

Most of the participants were aware that they could make a choice about where to give birth. This awareness was present even before they contacted or met the midwife, or accessed maternity services.

"I had already claimed the choice as soon as I found out that I was pregnant (...) I decided to have a hospital birth"

All participants experienced that the choice talk was part of a checklist at the first antenatal (booking) visit during which midwives introduced the topic and simultaneously enquired about women's preferences. The participants already had a strong preference where to give birth prior to this moment and therefore regarded it as somehow overdue. They also mentioned

Table 3: Examples of Analytical Coding.

Quote	Category	Theme
<i>"Having this choice is an obvious thing, isn't it? I never gave it much thought that I wouldn't"</i>	Awareness of choice	Choice talk
<i>"Why not ask again... talk about it... later on"</i>	Moment of information	Option talk
<i>"It was really good to pay some attention to it (...) the facts, pros and cons"</i>	Discussing pros & cons	Option talk
<i>"...and discussed pros and cons with my boyfriend"</i>	Decision support (partner)	Decision talk
<i>"...and with recognition of the midwife"</i>	Decision support (midwife)	Decision talk
<i>"I really appreciated it that she completely respected my choice, you know, never a moment of trying to change my mind or convince me to alter my decision"</i>	Attitude midwife	Decision talk
<i>"...the ultimate choice, uh, where, well, that is ours..."</i>	Perception	Decision ownership

that the topic overall did not receive a lot of attention or time.

"It was just a question of: 'You can choose where to give birth. Have you thought about it?' That's it. So, yes, I knew, I had already made a decision, and I told her... yeah, that was really it. Box ticked"

OptionTalk

Participants received information pre-dominantly during the first half of pregnancy. Most participants said that the midwife's option talk mainly included detailed information about the available places of birth options. This information was usually provided at the booking visit, simultaneously with the choice talk. A majority of the participants thought that the option talk was too early and sometimes even unnecessary. They perceived that things change during pregnancy (*i.e.*, complications), which may influence or change their initial decision. But above all, they had other priorities and concerns at the early stage of pregnancy.

"I know about the different options and what they involve, yes, but I don't give it a lot of attention just yet, there are other things that occupy me (...) work, where this baby is going to sleep"

All participants thought that their preferences need to be revisited, ideally in the third trimester, although none of the participants had changed their mind about their preferred place of birth during the course of pregnancy. They were, however, aware that there could have been a slight possibility that they would have changed their mind during the pregnancy.

"It was a bit weird, um, she [midwife] thinks I am having a hospital birth but she [midwife] never checked it [preference] again. As I say, weird; what if, say if, maybe I might change my mind. I don't know; why not ask again... talk about it... later on"

All participants had a very strong preference where to give birth prior to the option talk and did not specifically want information about options and consequences, as they had no desire to change their decision. Instead, they wanted more

tailored information, fitting parity. All participants experienced the option talk as a moment of confirmation or evaluation of their preference. The participants did not weigh options and consequences when talking to the midwife, but they merely revised the merit of their preference.

"It was really good to pay some attention to it [option talk], uh, not that I didn't know the facts, pros and cons etcetera, etcetera, or heard something new, but just, well, to put it [preference] into perspective"

Decision Talk

All participants mentioned that they had experienced an individual decision-making process considering their preferences and deciding what suited them best. The participants perceived that their partner had an active role in supporting the decision. Although they assigned the midwife a more passive role, all participants voiced a need for the midwife to acknowledge their choice.

Interviewer: "How did you know you had come to a final decision?"

Woman: "I had thought about it [preference], and discussed pros and cons with my boyfriend, and then it [place of birth] was completely clear. It [decision] was based on what I thought and wanted and a mutual understanding between him [boyfriend] and me... it suited us... and, yes, with recognition of the midwife"

Decision Ownership

All participants strongly emphasized that the *final decision* belonged to them and to their partner. Only when complications arose or in case of emergency, they thought it was the midwife's decision and responsibility to intervene with the woman's choice. The participants also perceived the *decision-making process* was owned by oneself and the partner. The midwife was only regarded to alter the decision about place of birth when referral became necessary.

“Yes, she [midwife] then takes the decision. (...) At that moment [when referral is necessary]. So, yes, in that case, yes, that situation than overrules my choice”

All participants voiced that shared-decision making about place of birth is a process that solely belongs to, and takes place between the woman and her partner; as main stakeholders and owners of the decision.

“Well, to my opinion the decision is something that belongs to me and ... [name partner], um, my husband. It is our decision. We eventually, uh, it is going to be our child, and yes, the birth of our baby will be supported by the midwife and she will help me, but uh, the ultimate choice, uh, where, well, that is ours...”

DISCUSSION

We explored the shared-decision making experiences about place of birth of Dutch pregnant women who received midwife-led care in order to better understand the features of this phenomenon. Shared-decision making regarding place of birth is considered to be a mutual process of the woman and her midwife.^{1,19} We appointed pregnancy or the antenatal care period as the course of making a shared decision about place of birth.^{2,8} As cross-reference, we fitted Elwyn's model¹ with its included steps over this designated period—aligning choice talk with the beginning of pregnancy and the initial contact with the midwife, the decision talk with the end of pregnancy/start of labour and the option talk fitting in between the two.²

Our findings confirmed that shared-decision making is indeed a bilateral process but—in our case—between the woman and her partner instead of the woman and the midwife, opposed to the theory appointing the midwife as the partner in the decision making process.^{1,19} Our findings also showed that women did not experience shared-decision making as a process consisting of a sequence of separate recognizable steps, but they experienced these steps to occur somehow simultaneously, blended and as iterative. Our findings also showed that choice talk, option talk and decision talk did not take place throughout the period that women received antenatal care, as the decision had already been made before the woman actually had met the midwife. These findings are consistent with women's decision making about breastfeeding.^{31,32} We identified an additional theme: Decision ownership. The women in our study claimed the decision as personal, concerning herself and her partner, as exclusive executives of the decision.

The decision about place of birth appears to be a topic with a personal character that requires a decision between the woman and her intimate and significant other (*i.e.*, *partner*), instead of a decision being made between the woman and a professional healthcare provider. This might be explained by the fact that women perceive that preparation for birth, including place of birth, is not a priority for midwives¹¹ and therefore make this decision with their partner. We need to consider that the period of pregnancy is a period of transition to parenthood for the

partner. This might explain why women put a stronger emphasis on the relationship with their partner as a future co-parent than on the relationship with their midwife. The underlying rationale supporting the achievement of shared-decision making relates to the character and quality of the interpersonal relationship and interdependency between people.^{1,33-35} Our findings suggest that these aspects play an important role in shared-decision making regarding the place of birth between the woman and her partner.

Women in our study dismissed the option talk with the midwife, they did however use this to validate their decision—although it did not change their preference, only when obstetric-led care was needed. Women apparently do not change their mind about place of birth when the pregnancy has a physiological course.⁸ We are not fully aware as to on the basis of what information women and their partners make their decision in this preconception period and further research to expand our knowledge about women's resources is therefore required. If midwives are involved earlier in women's lives, it might optimize women's breadth and content of information. It might not change women's preferences, as we know these are based on attitude that subsequently influences intention and thus preference.³⁶ However, it might contribute to incorporating option talk to a wider extent as currently described in our study. How to involve midwives at earlier stages in women's lives requires more research. Our findings underpin the importance of preconception care, where the midwife might be able to make better use of the three steps of the shared-decision making model³⁷ regarding place of birth. Therefore, it is worth to explore shared-decision making regarding place of birth among healthy women who have a pregnancy wish or are planning to become pregnant, in order to better understand the process.

Decision ownership contradicts with the midwives' perceptions that partners should not be involved in final decisions in care.³⁸ Decision ownership can also be regarded as a sign of autonomy.^{19,33} Ownership of the decision is also strengthened by the timing of the woman's decision making in our study, an event that took place before the initial contact with the midwife—a moment when there is an established communication between the woman and her partner, and not necessarily with the midwife. This suggests that it might be worth considering how women can become familiar with midwives even before they get pregnant.

STRENGTHS AND LIMITATIONS

To our knowledge this study is the first to explore women's experiences regarding place of birth by means of the practical usage of the shared-decision making model.¹ The findings expand our knowledge and understanding of some important features of this process. We reached a saturation point that no new findings were evident in the data. We transparently documented our strategies to enhance the credibility, transferability, dependability and conformability of our findings, including cross-referencing our research question throughout, member checking during and post interview, triangulation of the

interview data and field notes, peer debriefing and peer review, an audit trail of our analysis process, and purposive sampling techniques.^{25-27,30,39} However, our purposive sampling may have introduced selection bias because of its self-selective nature.^{30,39} All our participants had an outspoken preference for the place of birth, none of our participants were undecided. However, the participants were in the third trimester of their pregnancy and a decision regarding place of birth is expected to be made.^{2,8} We might have included women with a high sense of autonomy or more outspoken ideas¹⁹ about the choice regarding place of birth, likely affecting representativeness of our findings. Moreover, the timing of the interview in the third trimester of pregnancy when decisions about place of birth had been made much earlier, might have introduced recall bias.³⁹ Our focus groups were small which could have affected the dialogue dynamics. On the other hand, a small number of participants might have enhanced the feeling of group safety and therefore is likely to have increased self-disclosure of the participants.⁴⁰

Using the shared-decision making model¹ allowed us to understand the process better. The use of a priori model in constructing our topic list for the interviews increased the robustness of our study.⁴¹ Identifying an additional theme showed completeness of the data and contributed to better understand why shared-decision making about place of birth occurs at a different time than anticipated based on the literature.^{1,19}

The fact that women think that having a choice where to give birth is an accepted norm, can be a cultural aspect of maternity services where homebirth is still accepted as one of the realistic choice options.^{2,8} This might not be the case in other countries where options are sometimes limited or hospital birth is the only option. Therefore, this finding might not be generalizable to other populations of pregnant women. Additionally, all our participants were living with their partner and were between 27 and 38 years of age. The shared-decision making process of younger and single women about the place of birth might differ from those of women with characteristics similar to our study.³⁶ Our findings might therefore not be transferable to women from different ages and with other relationship status.

Participants were partly recruited by their own midwives and practice assistants. It is unknown how many women were approached and if women were consciously and categorically approached. This could have created selection bias.^{30,39} There is no information available of the midwifery practices; specifically, how and what information during the steps of shared-decision making is handled by individual midwives. Communication skills¹ and experience of midwives with shared-decision making,⁴² identified as influencing factors, might vary between midwives, as acceptance of shared-decision making is still evolving in maternity services.^{43,44} There is also evidence that the degree of involvement in decision-making regarding pregnancy and birth issues vary among women.³⁸ These factors might have introduced variance in midwives' application and women's experiences of the three steps of the model, which subsequently

could have influenced our findings.

CONCLUSION

Midwives have a more facilitating role rather than being an active partner in the decision-making process about place of birth. Applying the shared-decision making model to the antenatal care period does not align with women's timing and process of making a decision where to give birth. For midwives to be involved in the process of decision-making about place of birth, the steps 'talking about options' and 'providing information' about place of birth should be taken at the very beginning of care or early in pregnancy but ideally before that. This allows an interactive exchange of professional and personal information between the midwife and the woman. We have to emphasize that shared-decision making of place of birth has to be built on the midwife's communication skills, building rapport and structuring pre-conception and antenatal visits as well as considering the time of choice, option and decision talk. Decision support of the partner should not be underestimated.

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CONTRIBUTION TO AUTHORSHIP

YF designed the study, AB, EOH, and DdR collected and analyzed the data. YF drafted the article. All authors interpreted the data, contributed to discussion, and reviewed or edited the article. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. YF supervised the study and is the guarantor.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Premature Ovarian Insufficiency: Aetiology and Long-Term Consequences

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ABSTRACT

Premature ovarian insufficiency (POI) is characterised by premature cessation of ovulation/ menstruation for 4-6 months along with raised serum gonadotropin levels especially follicle stimulating hormone (FSH) (>40 IU/L) on two or more occasions >4 weeks apart. POI is a heterogeneous disorder resulting from various autoimmune, iatrogenic and metabolic factors, chromosomal or genetic mutations and infections. Premature loss of ovarian function in women with POI is associated with long-term psychosocial sequelae, infertility and major health complications. It is also associated with age-specific increase in mortality due to cardio-vascular diseases. Its occurrence has increased in recent years as more and more women now-a-days attain motherhood late, also there is increase in incidence of gynaecological malignancies and its successful management leading to increased risk of POI. This manuscript aims to highlight the recent advances in pathogenesis and management of POI. Literature regarding premature ovarian insufficiency, its incidence, pathogenesis, management and recent advances was searched from various English language journals, WHO, ACOG data, published peer-reviewed articles on PubMed, Medline, Embase and Google Scholar upto 2017.

KEY WORDS: Amenorrhoea; Menopause; Ovary; Ovulation; Stem cells.

ABBREVIATIONS: POI: Premature Ovarian Insufficiency; FMR1; Fragile X mental retardation 1; WHO: World Health Organization; AOAs: Antiovarian antibodies; APSs: Autoimmune Polyendocrine Syndromes; FSH: Follicle Stimulating Hormone; BMPs: Bone Morphogenetic Proteins; ESCs: Embryonic Stem Cells; MSCs: Mesenchymal Stem Cells; UCMSCs: Umbilical Cord Mesenchymal Stem Cells; ADSCs: Adipose-derived Stem Cells; FMR-1: Fragile X Mental Retardation 1.

INTRODUCTION

Premature ovarian insufficiency (POI) also known as Premature ovarian failure or Hypergonadotropic ovarian failure or Menopausa precece¹ is defined as a primary ovarian defect, characterized by an absent menarche (primary amenorrhea) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea).^{2,3} Characteristic features include cessation of ovulation or amenorrhoea for 4 months or more, hypoestrogenism (estradiol levels <50 pg/ml)⁴ and high serum gonadotropin levels,^{5,6} especially two serum follicle-stimulating hormone (FSH) levels (>4 weeks apart) in menopausal range^{7,8} (>40 IU/l).⁴

POI was previously known as premature menopause, but this term is a misnomer, as all women with POI do not always stop menstruating, neither do their ovaries shut down completely.⁸ In most women aged >40 years, there is a physiological decline in ovarian function with aging which is called as perimenopause/menopausal transition.⁹ Ovarian ageing resulting in ovarian failure and menopause is a continuous process^{5,10} and menopause is usually attained at 51 years (range 40-60 years).¹¹⁻¹³ The World Health Organization (WHO) defines menopause as permanent cessation of menstruation due to ovarian follicular activity loss.¹³

POI differs from menopause as, in POI unpredictable and varying degrees of ovarian functions are still present in 50% of women, and about 5-10% can even conceive and deliver child after diagnosis and treatment.^{7,8,14} It is a hypergonadotropic and hypogonadism state resulting from depletion/dysfunction of ovarian follicles due to either low initial numbers or accelerated loss.¹⁵ Premature loss of ovarian function leads to significant long-term psychosocial sequelae and major health complications.¹⁶ It also results in age-specific increase in mortality rate.^{17,18}

Based on the age of onset, POI can present itself as primary amenorrhea, without onset of menarche, or secondary amenorrhea after puberty.³ It is a continuum of disorders with four clinical states which are not permanent. Patients usually budge from one state to another in an unknown manner.¹⁹ These states are as follows:

1. *Occult POI* presents as unexplained infertility with normal baseline serum FSH levels.
2. *Biochemical POI* presents as unexplained infertility with elevated basal serum FSH levels.
3. *Overt POI* previously known as premature ovarian failure is characterized by elevated serum FSH levels with associated menstrual disorders like oligomenorrhea, polymenorrhea, and metrorrhagia.
4. *POI* is an extreme state of total primordial follicle depletion; an irreversible state characterized by anovulation, amenorrhea, infertility, and elevated gonadotropin levels.

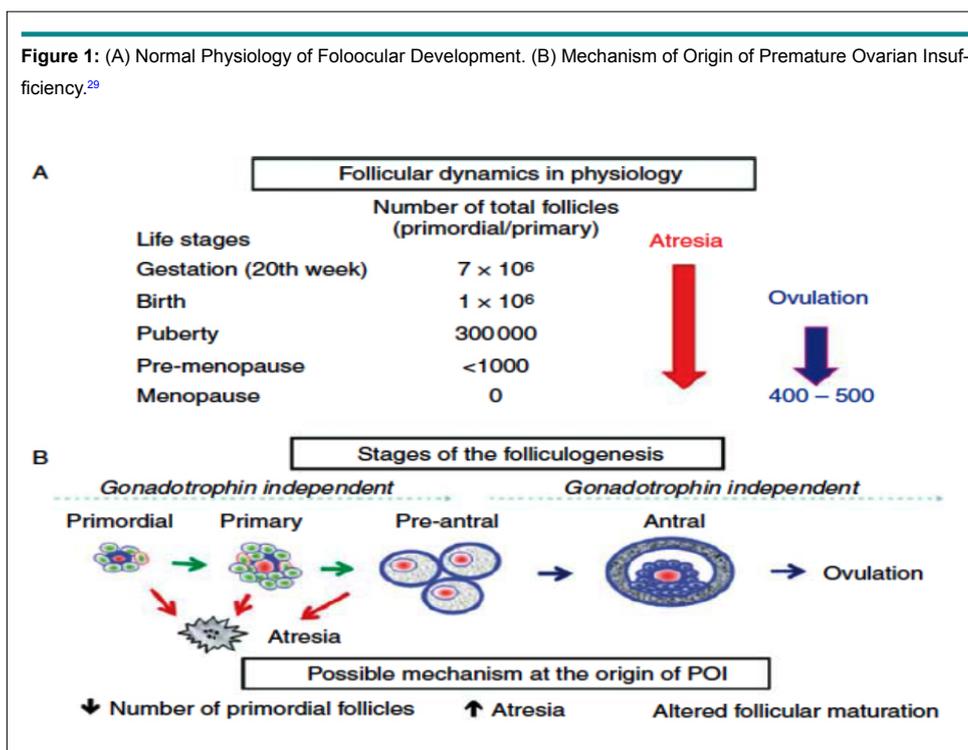
Incidence

POI is relatively common, with an estimated occurrence of 1 in 100 by 40 years; 1 in 1000 by 30 years^{11,12} and 1 in 10,000 by 20 years of age.^{1,20,21} It affects around 1-3% of women in the reproductive age below 40 years and around 0.1% in women below 30 years of age.^{2,10,18,22,23} Women with POI, around 10-28% experience primary amenorrhea and 4-18% secondary amenorrhea.^{10,18} Incidence of spontaneous onset POI has increased due to increasing success rates of cancer treatment in girls and young women.^{20,24,25} On the other hand, familial POI accounts for 15-30% of all cases.^{1,12,26}

Pathogenesis

Process of human folliculogenesis being highly complex and organised, is characterised by progressive maturation of small primordial follicles to larger ovulatory follicles. This whole process occurs continuously, and can stretch over a period of a year.²⁷ Reproductive life span of human females start with a fixed number of primordial follicles,²⁸ of which only 400-500 develop and ovulate before physiological menopause (Figure 1).²⁹

On the other hand, exact mechanism for development of POI is not known. It can be due to: a) Preliminary decrease in primordial follicle pool; b) Accelerated atresia of follicles; c) Defective maturation/recruitment of primordial follicles (Figure 1).²⁹ Furthermore, accelerated follicular atresia can be because of changed apoptosis rate, defective follicle maturation blocking and abnormalities in primordial follicle activation that causes decreased number of available functional follicles/accelerated



atresia.^{30,31}

Hence, factors that initiate such mechanisms are highly heterogeneous and can be a result of, genetic mutations, chromosomal, infectious, autoimmune, metabolic and iatrogenic factors.^{18,29}

AETIOLOGICAL FACTORS

Genetic Factors

Genetic factors are most commonly responsible for POI accounting for 7% of all cases.^{3,5,32} X chromosome is most commonly affected, but autosomal involvement is also common.^{18,33} Aneuploidies and rearrangements are most commonly reported with POI³⁴ (Figure 2).²⁹

X CHROMOSOME

Monosomy (45 X)

Terminal deletions of long arm of X chromosome result in primary amenorrhea and absence of breast development in all cases.^{12,35} Total or near total absence of single X chromosome,¹⁸ known as Turner's syndrome affects around 1 in 2500 live female births and is usually associated with ovarian dysgenesis leading to primary amenorrhea. However, 3-5% of such females with Turner mosaic karyotype can menstruate and even develop secondary sexual characteristics. Turner syndrome is associated with 4-5% POI cases.^{12,36,37}

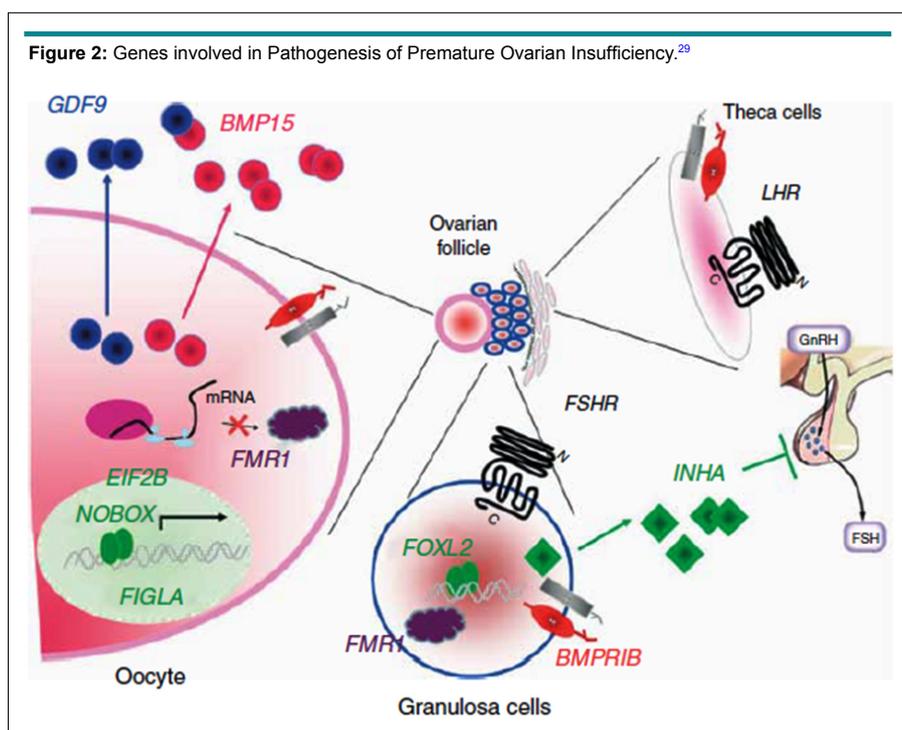
Trisomy

Trisomy affects 1 in 1000 women.^{12,18} Trisomy X females usually have normal ovarian function, but in some, it may manifest as early menopause, secondary amenorrhea, oligomenorrhea.^{10,38} Around 10% of females have mosaicism with 46, XX/47, XXX or 45, X/47, XXX karyotypes. Manifestations depend on time at which causing events occurred.¹⁰ Ovarian failure in females with 47, XXX (mosaic/non-mosaic) can be due to meiotic inadequacy of three X chromosomes, which is still unproven.^{10,34} However, cytogenetic studies in women with POI have shown that trisomy X (mosaic/non-mosaic patterns) have very low incidence of POI.^{10,39,40}

Fragile X Syndrome

Fragile X syndrome is an X-linked dominant genetic condition characterised by expansion of trinucleotide repeat⁴¹ with prevalence of 1/6000 in females and 1/4000 in males.^{42,43} It is a common cause of hereditary mental retardation and developmental delay.^{43,44} Fragile X mental retardation 1 (*FMR1*) gene is located on X chromosome at Xq27.3. There is expansion of CGG trinucleotide repeats in 5' untranslated region of first exon of *FMR1* gene. Affected females show >200 CGG repeats, as compared to normal (5-54 CGG repeats). This expansion of >200 repeats causes methylation-coupled silencing of *FMR1* gene resulting in loss of FMR-protein which is important for brain development in prenatal and postnatal period.^{41,43,45}

Recently, it was reported that higher number of CGG



repeats (>30-40) can be used to detect premature ovarian aging and POI in infertile women.^{43,46} An estimated 16-26% of female with *FMRI* premutation carriers develop POI,^{43,47,48} whereas only 2% of normal women develop isolated POI.⁴⁹ They are also known to develop tremor-ataxia syndrome,⁵⁰ mild neuro-cognitive dysfunction.⁵¹ It was also reported that paternally inherited Fragile X premutations were more likely to be associated with POI as compared to maternally inherited permutations.⁵²

Bone Morphogenetic Protein 15 Gene (BMP15)

Bone morphogenetic proteins (BMPs) are proteins belonging to transforming growth factor- β (TGF- β) superfamily, which play an important role in oocyte-specific growth/differentiation factors that help in follicle maturation and granulosa cell growth.^{18,29,53,54} BMP15 gene is located on the short arm of Chromosome X (Xp11.2) within 'POI critical region'.^{18,29,55} *BMP15* mutations are associated with 1.5-12% of POI cases.^{1,56-60} This defect is an unusual example of X-linked disease in which affected females inherit mutation from their unaffected father.^{1,56}

Autosomal Genes

Genetic studies have shown various isolated gene defects associated with POI, which are:

- a) Estrogen receptor (ER- α and ER- β) mutations,^{12,35}
- b) FSH receptor mutations (FSHR),^{61,62} associated with <1% POI cases.^{1,32, 60,63}
- c) LH receptor mutations (LHR)⁶⁴ associated with <1% POI cases.^{1,32,60,63}
- d) FOXL2 mutations: Occurs with either blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) type 1 (without POI) or BPES type 2 (with POI), known as POI-3.^{1,65,66}
- e) Steroidogenic factor 1 (NR5A1) mutation.^{12,35}
- f) CYP19A1 mutation.^{12,35,67,68}
- g) *Inhibin A* gene mutation associated with 5% of POI cases.^{60,69}
- h) *NOBOX* gene: Newborn ovary homeobox gene (*NOBOX*) plays role in initial phases of follicular maturation⁷⁰ and is rarely associated with POI.^{71,72}

Despite several genes shown to be associated with POI, the exact mechanism still remains uncertain.^{54,56,65,73}

Autoimmune Factors

Autoimmunity is characterized by auto-reactive lymphocytosis, organ and non-organ-specific autoantibodies.^{74,75} It accounts for 4-30% of POI cases^{1,8,76-82} and is characterised by presence of anti-ovarian antibodies (AOAs), lymphocytic oophoritis on histopathological examination, in association with other autoimmune conditions.⁸²⁻⁸⁶ Exact mechanism of autoimmune POI remains obscure and may be due to genetic and or environmental factors that are responsible for initiating immune response.^{43,75,83,87,88} Important factors involved are: Major histocompatibility complex antigen (HLA), cytokines, cell-mediated immunity, antibody-

mediated immunity, etc.^{43,75,83,87,88}

There are three main types of autoimmune POI: Adrenal autoimmune POI, non-adrenal autoimmune POI and isolated idiopathic POI.^{43,88,89} Autoimmune causes in pathogenesis of POI is characterised by presence of autoantibodies directed towards the ovarian tissue.^{84,90,91} These AOAs can be detected in the serum of affected females before clinical onset of POI.⁹² These antibodies bind to various steroid hormone-producing cells^{8,14, 82,93,94} like adrenal cortex cells, theca cells of ovary, placental syncytiotrophoblast cells, and are known as steroid cell antibodies (StCAs).⁸² They also bind to gonadotropins and their receptors,⁹⁵⁻⁹⁷ zona pellucid,⁹⁸ oocyte,⁹⁹ corpus luteum,^{84,100} and can act as markers of ovarian autoimmunity.⁸²

Furthermore, it was observed that POI has strong association with autoimmune Addison's disease. Around 60-87% cases of POI have Addison's disease.^{14,82,90,93,101} There are two types of autoimmune polyendocrine syndromes (APS)^{5,74,75} strongly associated with POI. Type 1 APS [autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)] characterized by combination of hypoparathyroidism, adrenal failure, and chronic mucocutaneous candidiasis. It is usually seen in children and is associated with POI in 60% cases presenting as primary amenorrhoea. Type II APS is characterised by autoimmune Addison's disease with adrenal insufficiency and other autoimmune illnesses without hypoparathyroidism.^{5,74} It usually occurs between the third to fourth decades of life and is associated with POI in 25-40% cases.^{14,82,90,93,101} Other autoimmune conditions commonly associated with POI are: hypothyroidism,¹⁰²⁻¹⁰⁴ autoimmune adrenal insufficiency,¹⁰⁵ hypoparathyroidism,⁷⁹ type 1 diabetes mellitus, hypophysitis, autoimmune haemolytic anaemia, celiac disease, inflammatory bowel diseases, glomerulonephritis,⁵ Sjogren's syndrome¹⁰⁶ and myasthenia gravis.⁸⁹

Iatrogenic

Iatrogenic causes for POI are increasing due to rise in incidence of various gynaecological cancers and their successful treatment.^{107,108} Oocyte is highly radiosensitive and responds to even 2 Gray dose of radiotherapy.^{43,109} Hence, an ovarian radiotherapy dose of ≥ 6 Gray results in ovarian insufficiency in almost all females over 40 years of age.¹¹⁰ Effect of radiotherapy on ovaries is dependent on dose, age, and radiation therapy field.^{43,111, 112} Chemotherapy also causes ovarian insufficiency but exact mechanisms are not clear; however, it is well known that chemotherapeutic agents affect granulosa cell functions and oocytes, ultimately causing ovarian insufficiency.^{43,113} Major predictive factors for development of ovarian insufficiency after chemotherapy are; age, class, dose of chemotherapeutic agent, concurrent use of radiotherapy, etc.^{43,108,114} It has been reported that use of alkylating agents (N-mustard, L-phenylalanine mustard, Chlorambucil, Busulfan, and Cyclophosphamide) are strongly associated with POI (40%).¹²

Furthermore, it has been reported that ovarian drilling for polycystic ovarian syndrome and chocolate cysts removal for endometriosis are associated with early menopause.^{12,115} Recent literature reports that uterine artery embolization also leads to POI by affecting ovarian vascular supply.^{43,116} Hence, it was observed that almost any pelvic surgery, be it ovarian cyst removal or hysterectomy—can affect ovaries and lead to POI, by affecting vascular supply or by causing inflammation in pelvic area.¹¹⁷ Studies have shown that in some cases of POI, ovarian function may return spontaneously many years after chemotherapy and/or radiotherapy^{118,119} and many successful pregnancies can also occur in such women.⁴³

Infectious and Toxic agents

Till date there are no direct evidences available that suggest correlation between infections and POI, but studies report that Mumps oophoritis may be related to development of POI. True reason of post-oophoritis ovarian failure is unknown.^{5,43,120} In vast majority of affected women, return of ovarian function occurs following recovery.^{18,43} Another infectious agent and its treatment that can be linked with POI is HIV infection.^{5,121} It has been reported that around 3.5% of females with POI have a history of infections like varicella, tuberculosis shigellosis, malaria and cytomegalovirus.^{7,43,80}

Amongst the various toxins that are strongly associated with POI, smoking is one major toxin. It was found that there is an inverse relationship between number of cigarettes smoked per day and age at menopause.^{43,122} Smoking causes alteration of ovarian function, and leads to early menopause in female who smoke as compared to non-smokers.^{43,123}

Other toxins that commonly affect ovarian functions and can lead to POI are: Polycyclic aromatic hydrocarbons (PaHs), toxic chemicals in tobacco, heavy metals, insecticides, plastics and industrial chemicals, but exact underlying mechanism is unclear.^{5,18}

Clinical Course

Women with POI are typically observed with secondary amenorrhea/menopause, many a times preceded by irregular menstrual cycle at age <40 years.^{20,78} In few women with primary amenorrhea, the cause can be an underlying chromosomal abnormality.²⁰ Other characteristic symptoms include hot flushes and night sweats^{20,124}; these are mainly due to estrogen deficiency.^{118,125} Vaginal symptoms include dyspareunia and dryness, which can be distressing for women.^{125,126} In addition to these, women also suffer from sleep disturbances, mood swings, lack of concentration, depression, loss of libido, dry eyes,¹²⁷ altered urinary frequency and lack of energy.^{117,125} These symptoms are usually transient and are mainly due to changes in ovarian functions (estrogen withdrawal rather than deficiency) that result from spontaneous onset of POI.^{125,128} Furthermore, it was observed that in women with surgically induced POI, symptoms are more severe

and persistent.¹²⁵

Diagnosis and Assessment

Diagnosis of POI can be easily made on clinical presentation, in woman <40 years of age with amenorrhea or oligomenorrhea of 4-6 months with two measurements of elevated FSH levels. Final diagnosis can be made on certain investigations which include¹²⁵:

Gonadotropin Levels: Both FSH and LH are elevated in women with POI (hypergonadotropic amenorrhea). Elevated FSH levels are more significant than LH. High FSH levels are considered as gold standard for diagnosis of POI and values >25 U/L on two occasions, more than 4 weeks apart is indicative of ovarian insufficiency.¹²⁵

Low Estrogen levels: Estradiol (E2) levels <50 pg/ml is typically observed in women with POI.⁷⁸ Low estradiol levels in combination with high FSH and LH levels are diagnostic of POI.

Antimullerian Hormone (AMH): AMH is homodimeric glycoprotein consisting of two subunits,^{129,130} and is produced by granulosa cells of growing follicles.¹³¹ It regulates early follicular recruitment from primordial pool¹³² and is a good reflector of ovarian reserve.¹³³⁻¹³⁵ AMH levels are usually very low or undetectable in women with POI.¹³⁶ Hence, AMH testing may become important diagnostic tool for assessment of ovarian reserve before and after chemotherapy in young women with pelvic cancers, before and after ovarian surgery, and for females at high risk of POI.^{137,138}

Inhibin B: It is produced by granulosa cells of growing follicles,¹³⁹ but its levels show significant variability between menstrual cycles. Hence, it is usually not recommended for diagnosis of POI.¹³⁸

Once diagnosis of POI is made, other investigations include:

- Karyotyping and fragile X mental retardation 1 (FMR-1) pre-mutation for genetic cause⁸
- Screening for autoimmune diseases like anti-adrenal, anti-21-hydroxylase,⁸ anti-thyroid peroxidase, anti-thyroglobulin antibodies¹²⁵ and AOA are recommended.

Future Fertility

Around 5-10% of women with POI conceive spontaneously due to fluctuations in ovarian functions.^{12,125,140} Till date no clear guidelines or drugs are available that can cause follicular development or increase fertility in women with POI.¹²⁵ Various studies have tried to examine the role of ovulation inducing drugs, gonadotrophins, glucocorticoids, GnRH agonists and antagonists,¹⁴¹ but no clear advantage has been observed.¹²

However, fertility preservation techniques can be considered for women at risk of developing POI due to disease or its management. Considerably high rates of natural pregnancies were reported in such women who underwent fertility preservation pre-treatment.^{125,142} Another way of improving fertility in women with POI due to sterilizing surgeries is replacement of cryopreserved ovarian tissue, but this has been studied in very few cases.^{125,143}

Recent advances have shown that oocyte donation is another option for women with POI desiring pregnancy.¹²⁵ Such a successful pregnancy was first reported in 1984¹⁴⁴ and since then it has become a 'routine' treatment.

Long-term Consequences of POI /Premature Menopause Bone Health

Estrogen is known for its beneficial effects on bone growth. It is responsible for increased bone remodelling and hence its deficiency is associated with bone loss, decreased mineral density and fracture risk, as seen after natural menopause.^{145,146} Net bone loss after menopause is usually 2-3% per year.¹⁴⁷ Effect of estrogen deficiency on bone in women with POI is one of most clearly recognized adverse effects of POI. It usually remains asymptomatic for many years, until fragility fracture happens. Furthermore, depending on degree and duration of estrogen deficiency, women with POI develop reduced bone mineral density earlier as compared to normal females.^{148,149} An estimated 8-14% of women with POI suffer from osteoporosis¹⁴⁸ as compared to normal females.¹⁵⁰

Cardiovascular

Estrogen has cardio-protective effects and its early loss leads to increased risk of cardio-vascular mortality.^{138,151} Hence, women with POI are associated with high risk of cardio-vascular mortality.^{78,125,138,151} Various researches have proven that women with spontaneous POI suffer early onset coronary heart disease¹⁵² and are at increased risk of dying from coronary vascular diseases (CVDs).^{125,153,154} Furthermore it has been observed that women with pre-menopausal estrogen deficiency develop signs of endothelial dysfunction¹⁵⁵ and premature atherosclerosis very early.^{125,156} It is well proven that estrogen plays an important role in ventricular contractile function,^{125,157} decreases insulin resistance^{125,158} and protects against lipid peroxidation, thereby playing an important role in cardio-protection.

Cognitive and Neurological Health

Few studies have observed the effects of POI on neurological health of women.¹²⁵ POI, especially the one resulting from bilateral oophorectomy before onset of natural menopause, increases risk of cognitive impairment/dementia. This risk is found to be inversely proportional to the age at which oophorectomy is performed.^{12,159,160} Such women are also prone to develop Parkinsonism later in their life.^{12,159,160} Hence, it is very important to explain all possible detrimental effects on neurological health

before planning for hysterectomy and/or oophorectomy in women <50 years, especially for prophylactic reasons.¹²⁵

Sexual and Genito-urinary Functions

In most women with POI, sexual problems are due to physiological stress, or secondary reaction to emotional stress of diagnosis and infertility resulting from the disease.¹⁶¹ Furthermore, fertility treatment has unpredictable outcomes which leads to emotional stress and affect sexual functions in the long run.^{125,162} Hence, to hold POI as the sole cause for sexual dysfunction may be incorrect, also there are no direct evidences to evaluate effects of POI on sexuality.¹⁶³

Most common symptoms are those related to estrogen deficiency, which include vasomotor symptoms, sleep disturbances, depression, fatigue, loss of libido, vaginal dryness and dyspareunia.^{125,164}

Endocrine Diseases

Women with POI are prone to develop endocrine disorders later in their life. Around 20% with idiopathic POI develop hypothyroidism and most commonly Hashimoto thyroiditis.²³ They also carry high risk of developing adrenal insufficiency.¹³⁸

Future Perspectives

Most recent studies have shown the role of stem cells in the treatment of POI and have reported that oocytes can be generated from embryonic stem cells (ESCs).^{165,166} These ESCs are induced into primordial germ cells which are then aggregated with somatic cells of female embryonic gonads for fertilisation.^{166,167}

Other pluripotent cells that have been studied for use include, mesenchymal stem cells (MSCs) used for repairing damaged ovaries induced by chemotherapy.¹⁶⁸ Umbilical cord mesenchymal stem cells (UCMSCs) can also be used with advantage of little or no immune rejection.¹⁶⁹ Adipose-derived stem cells (ADSCs) are another type of MSC that can be differentiated into multiple cell types.¹⁷⁰

Bone marrow transplantation has also been studied for use in women with poor ovarian function after long-term chemotherapy.^{166,171} Hence, it is possible that with the latest research and advancement, ovarian aging may become reversible in the future, especially in women with POI.¹⁷²

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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Opinion

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Towards Increasing Contraceptive Prevalence in Burkina Faso through Task Sharing

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The prevalence of contraception in Burkina Faso (BF) has increased in the past 18 years from 5.8%¹ in 1998 to 25%² in 2016; an increase of 1% per year while population growth remains strong and stable at 3.1% per year. The main reasons for such low progression of contraceptive prevalence include insufficient information on contraceptive methods, lack of competent providers and their inequality repartition in facilities, and inadequate sexual and reproductive health policies and standards.

In BF, the type of providers able to offer long-acting contraceptive methods (implant and IUD) according to sexual and reproductive health policies and standards are midwives, nurses and physicians. However, primary health workers (auxiliary midwives, auxiliary nurses) are the most active in the BF health system (about 40% of all categories). Contraception remains a good alternative for BF to pass the demographic transition and benefit from the demographic dividend in the coming decades.

One of the major strategies to significantly increase contraceptive prevalence in the coming years could be the task sharing in family planning. It involves allowing primary health workers to offer long-term contraceptive methods and Community Health Workers (CHWs) to offer oral and injectable contraceptives in their communities.^{3,4} Indeed, task sharing will significantly increase the supply of contraceptive services and approach services as close as possible to the population. The immediate impact of this strategy will therefore lead to increased contraceptive prevalence, thus reducing maternal and infant mortality, controlling population growth and the country's natural resources as a guarantee of sustainable development.

Although, task sharing in family planning has proved its efficacy in several other countries around the world, BF is still in the pilot phase of this strategy. Why invest in testing a strategy that has already proved its efficacy in several other countries?⁵ Is it not a waste of resources? These are some of the questions we ask ourselves about the political decision to implement the task sharing in the pilot phase in the context of scarce resources and accelerated population growth. BF would definitely benefit from going directly to scale up with this strategy. Meanwhile, as a result of this testing phase, several NGOs/projects are already jostling for the implementation of this promising strategy in their catchment area. It is now for Burkina Faso's Ministry of Health to grab this opportunity to increase the access of long-term contraceptive methods in each facility.

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Research

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Chronic Diseases during Pregnancy and Birth Outcome: A Study Based on Tertiary Hospital of Mumbai

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ABSTRACT

Background/Objective: Chronic disease has emerged as one of the most serious public health problems while disease prevalence during pregnancy had a greater risk of premature death and long-term illness. However, it is an important determinant of an adverse birth outcome like pre-term delivery, low birth-weight, premature delivery, stillbirths, perinatal morbidity and mortality. Hence, the study examines the chronic disease prevalence among women and its association with adverse birth outcome.

Methods: The study was conducted on inpatients' that came for delivery in a tertiary hospital of Mumbai from 20th January to 31st May 2013, by using semi-structured questionnaire. Questions were asked about chronic disease prevalence before and during pregnancy and the outcome of pregnancy.

Result: About 50% of women were reported of having some sort of chronic disease during pregnancy while severe anemia was the most common complication irrespective of pregnancy status. Women with any chronic disease during pregnancy have a higher risk of adverse birth outcome such as low birth-weight and pre-mature delivery, etc. Where a significant difference was found between women with chronic disease during pregnancy and without disease in delivering premature and low weight at birth baby.

Conclusion: Obstetric health complications are one of the major health issues that result in adverse maternal and perinatal outcomes, and it is very important to know about the complications and its consequences on birth outcomes. This will help to improve the health status of the mother and the newborn.

KEY WORDS: Chronic disease; Birth outcome; Low birth weight; Stillbirth; Mumbai.

INTRODUCTION

Disease prevalence during pregnancy has a particular importance in the study of maternal well-being and neonatal outcomes. Women in their reproductive age and with chronic medical conditions have a greater risk of not only pre-mature death and long-term illnesses but also for pregnancy complications. Therefore, it is not surprising that women with chronic diseases are often anxious about pregnancy.¹ Smoking, diabetes and hypertension increase the risk of pre-term delivery,² whereas, smoking and obesity has led to the risk of infant birth defects.^{3,4}

Chronic diseases and risk factors have been associated with maternal complications such as gestational diabetes, gestational hypertension and pre-eclampsia during pregnancy.⁵ Such previously existing complications or those developed during the pregnancy tend to get further aggravated by the physiological effects of pregnancy which may indirectly lead to maternal deaths.⁶ These include anemia, hypertension, diabetes, as well as infectious conditions of HIV and malaria. In developing countries, about 30% of maternal deaths occur due to indirect

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causes.⁷ The growing prevalence of lifestyle-related conditions contribute to the increased commonness of obesity. This also contributes to the growing list of health problems as obesity, diabetes mellitus, heart disease and hypertensive disorders.⁸ Women have also experienced increase in the prevalence of chronic disease related risk factors such as obesity, diabetes, high cholesterol, and asthma during the reproductive ages.⁹ Therefore, approaching women's health from a life course perspective offers an opportunity to reduce the pregnancy-related complications and deaths and to eliminate disparities through enhanced health promotion and disease prevention.¹⁰

Diabetes has become a global pandemic because of the sedentary lifestyle, urbanization and has lead to increased commonness of obesity.¹¹ In fact, a high prevalence of gestational diabetes mellitus (GDM) of the order of 18% has been reported in India.¹² Similarly, hypertension/high blood pressure has been found to be the most common chronic disease during pregnancy. It reduces the supply of oxygen and nutrients to the uterus, potentially slowing the child's growth and increasing the risk of low-birth weight.¹³

However, nutritional deficiency like anemia is not only leads to poor outcomes in pregnancy and reduced work productivity among adults, but also contributes to deaths among pregnant women. Levy et al¹⁴ in their retrospective study evaluated the pre-term birth and birth weights of the anemic pregnant women which has determined maternal anemia as an independent risk factor for poor birth outcome. However, severe anemia during pregnancy may also have adverse effects on the mother and the fetus.¹⁵

With an epidemiological transition started in India, the burden of chronic disease and non-communicable diseases is on the rise.¹⁶ It has been predicted that there will be a rise of 67% death among all deaths by chronic diseases in 2020, which was 53% in 2005.¹⁷ However, there is a dearth of literature on maternal chronic disease and adverse birth outcome among women from lower socio-economic strata in India. Hence, our study tries to examine the chronic disease prevalence among women and its association with adverse birth outcomes that belong to lower socio-economic strata of the population in Mumbai city.

Study Area

The population of Mumbai has significantly increased over the past few years leading to an alarming population amongst the slum dwellers too. According to census 2011,¹⁸ the population of Mumbai was 12 million and the number of people living in slum areas has also grown up by a staggering 3 million. Being a metropolitan city, the situation in Mumbai is different from other cities and a large percentage of population lives in the slum areas. Hence, the main aim of the study is to bring out the prevalence of chronic health complications among women and its adverse impact on birth outcome. Mainly among those from low-income households, living in slum areas, poor and not willing to utilize

the health facilities provided by the private health sector. In this context, a tertiary hospital was selected which is situated nearby the slum areas of Mumbai.

MATERIALS AND METHODS

Self-reported reproductive health complications of inpatients were collected through personal interviews in a tertiary hospital of Mumbai. A total of 300 inpatients were selected based on their consent for participation in the interview from 20th January to 31st May 2013. The interview was conducted on women (inpatients) that came for delivery at the selected hospital and are from the lower socio-economic strata of the population. The main focus was to access the prevalence of chronic diseases among women in the surveyed hospital. The patients were enquired whether they suffered from any chronic diseases at any time of their life, especially before or during pregnancy. Specific type of chronic diseases such as, diabetes, hypertension, anaemia, any cardiovascular diseases etc. are included in the questionnaire. Women were also asked about the treatment they received for their chronic illnesses. The self-reported chronic disease status was also cross verified with the hospital case sheets to know the disease status. Among the selected population 151 were having any disease during pregnancy while 149 does not reported of any disease status during pregnancy. Reporting of any chronic disease during and before pregnancy was taken as the dependent variable for the analysis where, 'having any chronic disease was taken as '1' if 'yes' and '0' if otherwise. For further analysis, all the reported diseases were grouped into three different categories, like women having at least one chronic disease, one to two chronic diseases and more than two chronic diseases during pregnancy.

The outcome variables of the study were low birth weight, prematurity, birth defects and other neonatal complications. However, to compare the pre-natal and perinatal outcomes, participants were categorized into groups according to the number of live births and previous pregnancies. So the participants were categorized into two groups; Primiparous and multiparous with chronic disease during pregnancy and primiparous and multiparous without chronic disease. Socio-economic and demographic characteristics of women were considered as independent variables for analysis to see the impact on health of the women and new-born. Both descriptive and analytic statistical methods were used. Frequencies and bi-variate analysis was performed to see the disease prevalence. Whereas, inference statistics was calculated using chi-square tests according to Pearson's coefficient.

Chi-square test was performed to explore the significance difference between the selected women and new-born health indicators. As Chi-square test is used to see the association between two classifications (classifier variable) of a set of counts or frequencies and compares the observed and expected frequencies in each category. Results are presented in terms of odd ratios and associated *p*-values. All the analysis was done using SPSS 20.

Ethical Approval

The International Institute for Population Sciences-Students Research Ethics Committee (IIPS-SREC) approved the study, and it was explained to the participants that the information collected was solely for the purpose of research and the confidentiality of their names would be maintained. The participants' verbal consent was obtained and recorded on paper. .

RESULTS

Demographic Profile of the Respondent

The mean age of the respondent is 25 years ($SD\pm 4.06$). The highest numbers of respondent (inpatients) were in the age group of 20-24 years (45.7%) whereas only 3.3% of respondent is in age below 20 years. The mean age at marriage of the respondent is about 20 years ($SD\pm 2.71$). More than half of the total respondents were married before completion of 20 years of

age (56.6%). The mean duration of marriage is around 6 years ($SD\pm 4.03$). Half of the respondents were married for less than 10 years. About 66% of women reported of having their first child at the age group of 20-24 years and the mean age at first birth was 21 years, whereas 32% of the births are of first ordered birth. Forty-nine percent are second ordered and 19% births are third or higher ordered birth. Out of the total births 52% were male and 48% were female child. Some preference was seen among the women as many of them reported that they gave birth of more than two or three children because they wanted a male child (Table 1).

Prevalence of Chronic Disease among Women

About half of the women reported having a chronic disease during pregnancy. Amongst all the diseases, anaemia (40.7%), respiratory disease (39.0%), hypertension (11%) and diabetes (9%) (Table 2) were found to be the most severe.

Table 1: Demographic Characteristics of Participants.		
Background Characteristics	N	%
Age of women (mean 25.25±4.06)		
Less than 20 years	10	3.3
20-24 years	137	45.7
25-29 years	100	33.3
More than 30 years	53	17.7
Husband's age (mean 29.61±4.84)		
Less than 25 years	27	9.0
25-30 years	175	58.3
30-35 years	64	21.4
More than 35 years	34	11.3
Age at marriage (mean 19.50±2.71)		
Less than 20 years	170	56.6
20-25 years	119	39.7
More than 25 years	11	3.7
Marriage Duration (Mean 5.73±4.03)		
Less than 5 years	132	44.0
5-10 years	135	45.0
More than 10 years	33	11.0
Age at first birth (mean 21.48±2.95)		
Less than 20 years	49	23.9
21-24 years	135	65.9
More than 25 years	29	10.2
Birth order		
One	96	32.0
Two	146	48.7
Three and more	58	19.3
Sex of the child		
Male	156	52.0
Female	144	48.0

Table 3 shows the socio-economic and demographic characteristics and its association with chronic disease prevalence among women. A negligible difference was found in reporting of having any chronic disease during pregnancy by age of the women. However, women in age group above 30 years reported more of having any chronic disease during pregnancy. Reporting of having any chronic disease, was found more among women with her second parity (52.1%). Meanwhile, more than three fifth of women reportedly underwent a C-section (Caesarean section) and about three-fourth had forceps delivery those were

having any chronic disease during pregnancy.

Women with any chronic disease during pregnancy reported to have had more antenatal check-ups compared to women without any disease. It is about half of the women who received proper antenatal check-ups during pregnancy as they needed more care and treatment with a disease. Similarly, highly educated women reported having more disease prevalence because they were aware of the symptoms of the diseases and its consequences compared to their counterparts. Ninety-eight

Table 2: Prevalence of Chronic Disease before and during Index Pregnancy.

Type of Chronic diseases	Disease prevalence among women			
	During pregnancy ¹		Anytime before pregnancy ²	
	N	%	N	%
No disease	149	49.7	90	30.0
Any chronic disease	151	50.3	210	70.0
Diabetes	14	9.3	4	1.9
Hypertension	16	10.6	77	36.7
Severe anemia	61	40.7	120	57.1
Tuberculosis	21	13.9	109	51.9
Cardiovascular disease	3	2.0	0	0.0
Respiratory disease	59	39.0	33	15.7
Malaria	5	3.3	88	41.9

Note: ¹Reported chronic disease by women were cross-checked with case-sheets
²Self-reported disease prevalence

Table 3: Type of Chronic Disease Prevalence among Women during Pregnancy (most Recent Birth) by Socio-Demographic Characteristics.

Characteristics	Any chronic disease during pregnancy
Age of women	
Less than 20 years	50.0
20-24 years	47.7
25-29 years	52.2
More than 30 years	54.7
Parity of women	
One	49.0
Two	52.1
Three and more	48.3
Type of delivery	
Normal	49.8
C-section	61.5
Forceps	71.4
Number of ANC visit	
Only once	43.8
2-3 times	43.4
More than 3 times	53.1
Women's education	
Primary	57.1
Secondary	49.2
Higher	58.6
Working status	
Working	30.0
Not working	51.0
Religion	
Hindu	48.1
Muslim	52.9
Treatment received	
Yes	98.0
Total	50.3 (151)

percent of women received treatment for their chronic diseases during pregnancy and most of them were treated in public hospitals.

Association of Chronic Diseases and Birth Outcome

Result demonstrates that most of the newborns with low birth-weight were delivered by women with who suffered from a chronic disease during pregnancy (33.4%), than women without any disease (26.4%) ($c^2=0.71$; $p<0.10$). Similarly, smaller size at birth (14.4%) and pre-mature delivery (10.6%) was also found to be high among women with any chronic disease during pregnancy ($c^2=0.84$; $p<0.05$). However, the result clearly shows that women having any disease during pregnancy have higher chances of delivery in C-section (11.3%) and with the help of forceps (13.2%) compared to women not exposure to any disease during pregnancy, which is 3% and 5% respectively.

But, newborns with birth defects were found to be higher among women without disease during pregnancy. The study results did not show any differentials in reporting of still-birth among women with any chronic disease during pregnancy

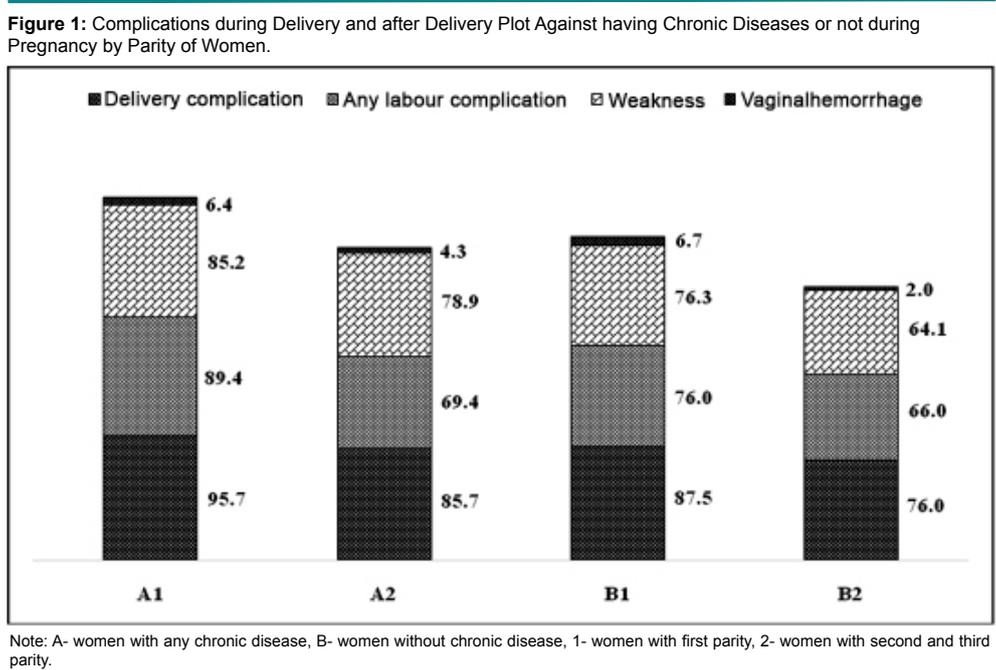
or not (Table 4).

The gestational month of delivery was also seen less among women who had any chronic disease during her pregnancy (i.e., delivered before completion of nine months). About 11% of the women delivered within seven months of gestational period and with chronic disease during pregnancy ($c^2=0.84$; $p<0.05$). However, no significant differential was observed in reporting of experiencing stillbirth and neonatal mortality. The study shows that women with any chronic disease during pregnancy had a poor health status of the newborn.

Figure 1 represents some of the specific complications during the time of delivery and after delivery among women who had developed any chronic disease during pregnancy. It also provides information by parity of women such as women having chronic disease or not with first parity and having chronic disease or not with her second and more parity in the studied area. It clearly shows that women having any chronic disease irrespective of first or second and more parity are more prone to having any complication at delivery as compared to women without chronic disease during pregnancy and about 96% with

Table 4: Outcome of Pregnancy by Chronic Disease Status of Women during Pregnancy			
Birth outcomes	Disease prevalence among women during pregnancy		c²
	With any Chronic disease	Without any Chronic disease	
Weight at birth			
Less than 2.5kg	33.4	26.4	
2.5 kg to 3.5kg	16.8	14.9	0.71*
More than equal to 3.5 kg	49.8	58.7	
Size at birth			
Smaller than average	14.4	12.2	
Average	84.1	87.8	3.48
More than average	1.5	0.0	
Type of delivery			
Normal	75.5	91.2	
C-section	11.3	3.4	4.86*
Forceps	13.2	5.4	
Gestation month at delivery			
Seventh month	10.6	7.4	
Eight month	14.3	14.1	0.84**
Nine month	75.1	78.5	
Any birth defects			
Yes	2.9	3.4	
No	97.1	96.6	0.50
Birth outcome			
Live birth	98.7	98.6	
Stillbirth/Neonatal death	1.3	1.4	1.33*
N	151	149	

Note: p values ***<0.01, **<0.05, *<0.10



first parity and 88% with second or more parity respectively.

Women with their first parity were observed to have experienced more complications like labor complication and weakness during and after delivery compared to their counterparts. However, chronic disease prevalence was another most important cause of health complications among women as reported by them. It was also observed that, any health complication during pregnancy was highly reported by women those who were not suffering from any chronic disease during pregnancy. Whereas in both the groups, vaginal hemorrhage was found to be higher among women having chronic diseases.

Table 5 represents the groups of chronic disease prevalence before and during pregnancy and its relation to the newborn health complications. Difficulty in breast feeding among newborn was highly reported by women with any chronic disease at any time before and during pregnancy. While it was seen more among those having any chronic disease any time before pregnancy (58.4%) than others. Breathing problem was found to be high (16.9%) among newborns whose mothers developed chronic diseases during pregnancy, while about 4 point less (13%) among those had chronic diseases at any time before pregnancy. Low weight at birth and baby develop yellow staining on palm and soles were also found high among women

Table 5: Newborn Health Complication by Chronic Disease Prevalence of Women (before and during Pregnancy).

Newborn health complications	Prevalence of any chronic disease among women	
	During pregnancy ¹	Any time before pregnancy ²
Low weight	22.0	20.8
Feeding problem/Poor sucking	56.8	58.4
Problem in breathing	16.9	13.0
Dull and inactive	5.1	5.8
Yellow staining on palm and soles on body	13.6	11.1
Cold/cough	16.9	16.3
Ulcers in mouth	12.7	7.8
Any other problem	55.1	58.8

Note: ¹Reported chronic disease by women were cross checked with case-sheets
²Self-reported disease prevalence

with disease prevalence during pregnancy compared to their counterpart.

DISCUSSION

The main aim of the study is to bring out a brief overview of chronic disease prevalence during pregnancy and its association with the health of women and the health of the new-born. Half of the women were suffering from a type of chronic disease during pregnancy whereas about three-fourth of them reported having any chronic disease at any time in lifetime. Severe anaemia (40.7%) and chronic respiratory illness (39.0%) were the most common diseases found among women. Study by Kersten et al¹ has found that every fifth pregnant woman suffers from at least one chronic disease, and higher prevalence rates have reported in the literature. In an American study analyzing 6294 women of childbearing age, 26.6% of the participants had one of the most prevalent chronic diseases. In contrast, 39.1% of all women who were not pregnant reported that they were chronically ill.¹⁹ While our study shows that about half of the women reported of developing any chronic disease during her pregnancy.

Severe anemia is not only concentrated among women at pregnancy but also before pregnancy that continues to be a major public health problem. It has been estimated that more than one-third of the world's women are anemic; the vast majority of this being in developing countries.^{20,21} It is generally agreed that the prevalence of malaria is higher among pregnant women than other groups, and that can lead to abortion, intrauterine fetal death, pre-mature delivery and even maternal death.²² Whereas, the prevalence of malaria was found to be most common among women, although, not particularly during pregnancy. Study shows that women having more than one or more than two chronic disease at the time of pregnancy has a higher chance of experiencing complications like labour related complications, convulsion (not from fever) during delivery. Where the educational status of women and receiving any antenatal check-ups has no positive association with developing any chronic disease during pregnancy as disease prevalence is quite hazardous to the weak immune health.

The study also highlights the women's chronic ill status and its association with the health of the new-born. A positive correlation was found between the mother's ill health status and adverse health outcome of new-born. While women with severe anaemia and severe respiratory illness also reported of delivering new-born with poor health status. Similarly, low weight at birth (54.1%), small sized baby (55.0%) and premature baby (66.7%) were delivered by the women who developed any chronic disease during her pregnancy compared to women without disease. So, it can be summarized that there is a positive association between mother's chronic ill health during pregnancy and adverse health outcome of the new-born. Chronic disease among pregnant women such as severe anemia has a significant influence on adverse pregnancy outcome.¹ Similarly, in our study we have found that a newborn with low birth weight, small size at birth

and premature birth were delivered by women who developed any chronic disease during pregnancy.

CONCLUSION

This analysis was done on hospital-based study in which the prevalence of all major chronic diseases during and before pregnancy was included as reported by the inpatients. Half of the women suffered from at least one chronic disease during pregnancy. In addition to this, the perinatal outcome appears to be less favourable for newborns of women with chronic diseases.

LIMITATION

The previous chronic history was taken based on the women's self-reported response. There were no clinical records to verify the previous history.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Review

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Treatment of Leg and Foot Edema in Women

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ABSTRACT

Several body systems, including the circulatory system, lymphatic system and kidneys, help maintain the appropriate balance of fluids in the body. A problem with any of these systems can contribute to the retention of fluid. Leg and foot edema, caused by the accumulation of fluids in tissue, is known as peripheral edema. Many women have been suffering from leg and foot edema reportedly. In the present review, we describe several methods of treating leg and foot edema in women, such as leg elevation, water immersion, bandage, stocking, foot massage, intermittent pneumatic compression, taking rutoside, reflexology and monitoring the interstitial fluid movement.

KEY WORDS: Foot edema; Legs elevation; Water immersion; Bandage; Stocking; Foot massage; Intermittent pneumatic compression; Rutoside; Reflexology.

INTRODUCTION

Leg and foot edema is caused by the abnormal fluid retention in the tissues of the lower extremities. The medical terminology for leg and foot swelling caused by excessive fluid collection is edema. This edema, caused by the accumulation of fluids in tissues, is known as peripheral edema. Due to the effects of gravity, edema occurs mainly in the lower extremities. Problems with the circulatory system, the kidneys or the lymphatic systems can contribute to the retention of fluids.

Leg and foot edema is a frequent and unpleasant accompaniment to pregnancy, causing pain on foot strike in severe cases. Though leg and foot edema arising solely from venous insufficiency is not in itself dangerous, it can lead to symptoms in women such as pain, feeling of heaviness, night cramps and paraesthesia leading to anxiety and ultimately seeking treatment. Chronic lymphedema is considered to be a progressive condition regardless of it being classified as primary or secondary which cannot simply be described as an accumulation of protein-rich fluid. Lymphedema progresses through stages (stage 0: also known as latent stage or subclinical stage of lymphedema, stage I: also known as pitting or reversible stage, stage II: also known as spontaneously-irreversible stage, stage III: also known as lymphostatic elephantiasis), and treatment intervention in early stages (stage 0 and stage I) has been shown to result in very good treatment outcomes if managed appropriately.¹

In this article, we describe several methods for treating subcutaneous edema in the legs and feet of women. Therefore, we need to know the treatment mechanisms to select a better one. Therefore, these treatments focus on recognizing and treating the cause of the fluid accumulation or on moving the fluid from the extravascular spaces of subcutaneous tissues.

TREATMENTS

Leg Elevation

If a woman with no obvious disease experiences swelling of the legs and feet, she should el-

elevate her legs above the level of her heart to keep the swelling down using gravity.^{2,3} For swollen legs and feet caused by pregnancy, pregnant women should also elevate their legs and avoid lying on their back in order to help improve the blood flow and reduce the swelling. The subcutaneous extravascular fluid in the legs and feet should then move toward the pelvis.

Water Immersion

Hydrostatic force is proportional to the depth of immersion. As the pressure gradient increases with depth, this hydrostatic pressure causes an inward and upward squeezing action on the body. It is this mechanism that causes the effects of buoyancy. The buoyancy reduces the gravitational load on the body, meaning objects such as the human body weigh less when in water.⁴ Therefore, deep immersion compresses the leg and foot skin and acts on the fluid in the extravascular spaces uniformly from all sides. Subcutaneous edema fluid is pushed from the extravascular space into the venous system, and extravascular fluid can be moved by water aerobics.^{5,6} Kent et al⁷ experimented on pregnant women standing in water up to the axilla (static immersion) or in low-intensity water aerobics class, also with immersion up to the axilla. They reported no marked difference in the diuretic effects of static immersion and water aerobics. Water aerobics and static immersion had similar effects on the urine specific gravity. This result implies that a water aerobics class will offer the same diuretic and edema-reducing benefits as simple immersion in the same depth of water.

Hartmann and Huch also researched the response of pregnancy leg edema to a single immersion exercise session.⁸ They concluded that a single immersion exercise session was a simple and cost-effective method of treating and preventing the unpleasant but common, symptom of pregnancy edema. However, the duration of the volume-reduction effect of immersion exercise is unclear. Further studies are necessary to investigate the duration of its effect.

Bandages

Bandages can exert high pressure on the subcutaneous tissues of swollen legs and feet.^{9,10} Mosti and Partsch¹¹ reported that an inelastic bandage exerted about 60 mmHg compression. Such compression can quickly reduce edema by pushing the subcutaneous edema fluid from the extravascular space into the venous system. In order to maintain the edema alleviating effect, after being treated with a non-stretchable dressing, women should wear elastic stockings, as inelastic bandages lose pressure in the supine position very quickly, mainly as a result of edema reduction.¹² In contrast to inelastic bandage, an elastic bandage has a high resting pressure and a high working pressure.¹³ Elastic systems are not safe for coexisting arterial diseases. Little pressure is lost over time.

Bandages have been shown to be well tolerated and produce no pain. Mosti and Partsch¹¹ concluded that the edema

reduction effect of bandages was equal to that of double stockings.

Stockings

The pressure of an elastic stocking on the swelling skin is less than that of a bandage. At rest, stockings generate an almost constant pressure known as the resting pressure, and with movement, such as when walking, the stockings generate variations in pressure.¹⁴ Mosti and Partsch¹¹ reported the following: in patients with venous leg edema, a compression pressure of around 20 mmHg exerted by a stocking led to a reduction in edema comparable to that achieved by an inelastic bandage applied with a pressure of around 60 mmHg when both systems were worn day and night for 1 week. External compression increasing the tissue pressure may reduce the capillary filtration. A stocking with a very low pressure may therefore be sufficient to obtain an effect of reducing the capillary filtration.

In addition, Carvalho et al¹⁵ reported that using elastic stockings during the entire day reduces the edema and pain in patients with signs and symptoms of chronic venous disease classified as a Clinical, Etiology, Anatomy and Pathophysiology (CEAP) classification of C3 (swollen ankles edema due to varicose veins or hidden varicose veins-venous reflux).

Foot Massage

Foot massage is an example of an intervention can be used for specific conditions, such as leg and foot edema, as it moves extravascular fluid without disturbing the intravascular fluid.^{16,17} However, some subcutaneous edema fluid may be pushed from the extravascular space into the venous system. Foot massage involves the manipulation of the soft tissue of the foot and is more general and does not focus on specific areas that correlate with other body parts, in contrast to reflexology.^{16,18} In their study, Çoban and Şirin¹⁹ found that a 20 min foot massage daily for 5 days significantly reduced the physiological lower leg edema during late pregnancy.

Manual Lymph Drainage (MLD) massage is often helpful in reducing edema because it stimulates blood flow, fluid movement and lymphatic system function (detoxifying our bodies). MLD massage strokes are often made in upward motions toward the heart to encourage the lymph movement.²⁰

Intermittent Pneumatic Compression

In advanced stages of lymphedema, tissue fluid spaces can also be found in thickened perimuscular fascia. Since there are no forces capable of mobilizing and propelling stagnant fluid to the regions where lymphatics can absorb them, this task should be performed by external massage. The most effective method is sequential intermittent pneumatic compression (IPC).²¹ Since the lymphatic collectors are obliterated, fluid cannot be pushed into these points, and alternative paths must be created. Olszewski et

al²² showed that, in lymphedema, high external forces move fluid along anatomical structure, but not lymphatics. Zaleska et al²³ said that stagnant fluid should be propelled toward the root of the limb. IPC generates effective transmural pressures, overcoming the low hydraulic conductivity of the subcutaneous tissue, securing unidirectional proximal flow, and preventing backflow. Zaleska et al²⁴ also found that long-term external limb compression using an IPC device resulted in an increase in the tissue channel cross surface area in the thigh, with a concurrent decrease in the circumference of calf. Their observations suggest that the new channels developed in such areas as the upper thigh, hip, and lumbar with a normal lymphatic drainage. Those authors then hypothesized that IPC replaces the missing lymphatic function by providing a fluid-moving force, subsequently enhancing the channel formation process and, in effect, facilitating the evacuation of fluid containing excess cytokines, including those that upregulate collagen synthesis.

Rutoside

Rutosides are a group of compounds derived from the horse chestnut (*Aesculus hippocastanum*), a traditional herbal remedy for treating edema formation in chronic venous insufficiency.²⁵ Cesarone et al evaluated the effects of hydroxyethyl rutoside at a dose of 1 g/day on the prevention and control of flight microangiopathy and edema in subjects with varicose veins and moderate chronic venous insufficiency when flying for more 11 h.²⁶ They concluded that hydroxyethyl rutoside (at 1 g/day) was useful and effective in reducing the increased capillary filtration and in controlling leg edema in patients with venous hypertension on long-haul flights. In brief, hydroxyethyl rutoside controls distal edema in venous hypertension and also improves the microcirculation by improving the venoarteriolar response and by controlling the capillary filtration rate.

Bergstein²⁷ investigated the effect of hydroxyethyl rutoside in pregnant women with varicose veins. The number of patients reporting subjective improvement in the active drug group was significantly greater than in the placebo group. The patients receiving hydroxyethyl rutoside had a decreased leg circumference at the end of the study. Throughout the eight-week period of the trial, there were only minimal side-effects, and healthy babies with good Apgar-scores were delivered.

Reflexology

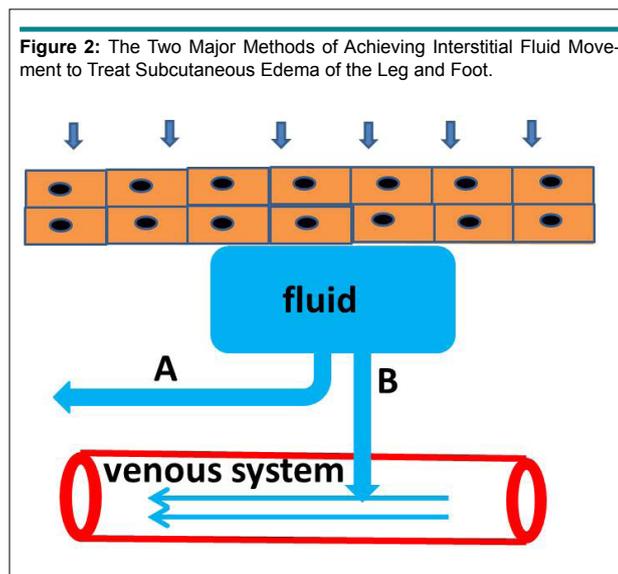
Reflexology involves the application of pressure to reflex areas of the hands or feet to produce specific effects in other parts of the body. The thumb and finger technique used differs from massage and resembles a caterpillar-like movement (Figure 1). Reflexology is not a new therapy, and evidence exists to suggest it was used for healing by the early Chinese, Egyptians and North American Indian tribes.²⁸ Early in the 20th century, a United States ear, nose and throat specialist, Dr. William Fitzgerald, observed that applying pressure to specific areas of the hands and feet resulted in an anaesthetizing effect on other specific areas of the body.²⁹ Using these findings, he divided the body into 10 longitudinal zones (5 on each side of the body) terminating in the toes and fingers and suggested that a direct link existed between these areas and the organs of the body within a given zone.

Reflexology is a complimentary natural healing therapy that can help the body, mind and soul on many levels and can definitely help in reducing swelling in the feet as the reflexes of the feet receive acupressure treatment during their session.³⁰

The lymphatic reflexology technique can be used to treat specific conditions, such as leg, foot and generalized edema, as it moves extravascular fluid without disturbing the intra-

Figure 1: Reflexology is the Gentle Manipulation or Pressing of Certain Parts of the Foot to Produce an Effect Elsewhere in the Body.





vascular fluid.^{31,32} The technique mimics the lymphatic drainage action of the body, i.e. interstitial fluid moves from the lymphatic capillaries to the lymphatic veins and trunks and returns to the circulatory system at the subclavian vein.³²

Mollart³³ studied the effects of lymphatic reflexology techniques, relaxing reflexology techniques and a period of rest on ankle and foot edema in late pregnancy. The finding indicate that the lymphatic reflexology techniques (and to a lesser extent relaxing reflexology techniques) have a non-significant clinical effect on reducing ankle and foot edema compared with a period of rest. However, participants perceived the lymphatic reflexology technique as being more effective in symptom relief than relaxing reflexology or a period of rest. A large percentage of lymphatic reflexology technique recipients have reported noticing less swelling and tightness in their feet after a session than relaxing reflexology recipients and rest recipients. Reflexology significantly assisted women in coping with symptoms in late pregnancy with a reduction in the levels of stress, tension, anxiety, discomfort, irritability, pain, and tiredness.

Here is an effective edema protocol that Moshe shared at the recent Reflexology Association of America conference.³⁴ It is a good preventative procedure for pregnant women and excellent when edema exists for any reason. If the edema is a result of an injury to the foot, then be very careful with the first two steps. Move the joints slowly and only so much as to not inflict pain on the individual. 1: Many repetitions of Pump – fast dorsiflexion. 2: Rotate the ankle joint, many times in both directions. Take through the full range of motion. 3: Specific attention has to be paid to the urinary, lymphatic and colon reflexes. Lymphatic reflexes are worked distal to proximal.

Botting showed that a few studies of reflexology have been performed abroad, but English translations of the full research reports are not readily available to allow for a critical

analysis of their methodology.²⁹ In addition, studies reported in the ‘gray literature’ (gray literature: “That which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers”) suggest that reflexology may be an effective treatment, but these are small-scale studies with inadequate description of the details of the methodology. Therefore, collaboration between reflexologists and experienced researchers should be encouraged, as good-quality studies are required to determine the effectiveness of reflexology.

CONCLUSIONS

We have roughly described two major ways of achieving interstitial fluid movement in the treatment of subcutaneous edema of the leg and foot (Figure 2). One way involves fluid movement in the extravascular space (Figure 2-A). Another involves fluid movement from the extravascular space into the venous system (Figure 2-B). The methods of leg elevation, foot massage, intermittent pneumatic compression and reflexology mainly move interstitial fluid in the extravascular space. In contrast, the methods of water immersion, bandage, stockings and taking rutoside mainly move interstitial fluid from the extravascular space into the venous system. All of these approaches can result in diuresis. Knowing these mechanisms, the effects depend upon the thoughtful selection of the best available treatment.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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