

Clinical Drug Trial Participation: Perspectives of Pregnant Women and Their Spouses

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Objective: This study aimed at investigating the factors influencing clinical drug trial participation by pregnant women and their spouses.

Methods: This hospital-based cross-sectional study was conducted at Women's Hospital, School of Medicine, Zhejiang University, from July to September 2020. A self-administered questionnaire was distributed to pregnant women and their spouses in the maternity ward. The questionnaire consisted of two sections: The first part was aimed at collecting demographic information data while the second part consisted of 10 open-ended questions regarding clinical drug trial knowledges, financial compensation, risk awareness, psychological impact, and pregnancy outcomes.

Results: A total of 206 questionnaires (115 from pregnant women and 91 from their spouses) were included in the statistical analysis. About 50% of pregnant women and their spouses had heard of clinical trials (50.43% vs 49.45%, $p=0.888$). Compared to their spouses, the proportion of pregnant women who thought that there is a need for the development of drugs during pregnancy was significantly higher (94.78% vs 16.48%, $p=0.008$). Moreover, a significant number of full-time employed pregnant women believed that clinical drug trials will increase the possibility of disease cure, relative to part-time/not employed pregnant women (98.21% vs 88.13%, $p=0.030$). Spouses whose education levels were below high school and those whose education level was high school or above exhibited significant differences regarding whether financial compensation will motivate their participation in clinical trials (77.78% vs 58.90%, $p=0.044$). Pregnant women and their spouses had no significant differences regarding various aspects: drug treatment during pregnancy, clinical trial drugs should be free, the need to increase the protection of pregnant women in clinical trials.

Conclusion: Due to fetus-associated concerns, most pregnant women are reluctant to be included in clinical trials. However, pregnant women and their spouses agree that medical treatment should be accessible for illnesses during pregnancy, and clinical drug trials during pregnancy should be performed. The usage of untested or sub-therapeutic drug regimens in clinical practice paradoxically increases the risk for fetuses. When recruiting pregnant volunteers for clinical drug trials, researchers should conduct in-depth consultations and comprehensively inform the pregnant women and their families on the pros and cons of their involvement.

Keywords: pregnancy, clinical trials, drug safety, participation, attitudes

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Introduction

Although pregnant women have concerns regarding drug safety, many of them take medications during pregnancy due to illness or pregnancy reactions. During pregnancy, about 58% to 97% of women take at least one drug.¹ The safety and



effectiveness of the drugs used by pregnant women should have been proven, and more than half of pregnant women and their spouses have perceived needs for information about the safety and use of medications during pregnancy.² However, the vast majority of newly marketed drugs have no reported human pregnancy experience. This is because pregnant women are routinely excluded from clinical trials because of ethical considerations and the fear of potential fetal harm.^{3–5}

In the past few decades, bioethicists, pharmacologists, regulators, and researchers elucidated on the need to include pregnant women in clinical trials to improve knowledge regarding the safety, dosage, and long-term effects drugs on pregnant women.^{6–8} Medical associations and regulatory agencies in various countries have been advocating for the removal of obstacles for pregnant women to be included in drug clinical research.^{6,7,9} The US FDA passed the “Pregnancy and Lactation Labeling Final Rule” (PLLR, Final Rule) in 2014. The rule requires an evaluation of the available information about a product’s use in pregnancy, which is expected to advance the development and implementation of clinical research on pregnant women.¹⁰ “Review Methods of Biomedical Research Ethics Involving Human Beings” passed by the National Health Commission of China emphasize on the protection of pregnant women and fetuses,¹¹ but there is no precise method or plan in the document. Currently, there are no published laws or guidelines for drug clinical trials involving pregnant women in mainland China.

The willingness of patients to participate in a given clinical trial is a sine qua non for that trial to be conducted. However, it is exceedingly challenging to recruit pregnant women as study participants because that a majority of pregnant women are the fear of potential fetal harm and lack of knowledge in clinical experiments.^{12,13} At present, there are few studies on the motivation of pregnant women to participate or not to participate in clinical trials, especially the views of pregnant women’s spouses. Thus, the principal objective of this project was to investigate the attitudes of the pregnant women and their spouses about participation in clinical trials to determine if this is one of the barriers to the involvement of this population in clinical trials.

Materials and Methods

Study Sample

Pregnant women and their spouses in the maternity ward of Women’s Hospital, School of Medicine, Zhejiang

University were invited to participate in the questionnaire survey. This survey was conducted from July to September 2020. Pregnant women and their spouses (age >18 years) who agreed to participate in this study were enrolled. However, pregnant women or their spouses whose physical or mental health (including reading difficulties and dysgraphia) prevented them from providing information were excluded.

This study was conducted in accordance with the Declaration of Helsinki.¹⁴ Signed informed consents were obtained from all participants. Ethical approval was obtained from the Ethical Committee of Women’s Hospital, School of Medicine, Zhejiang University (Ref: IRB-20200182-R).

Study Design

The study purpose and procedures were carefully explained to all participants by three trained study staff, and any questions were answered. Based on current literature, the questionnaire was developed by the investigators and pre-tested before the baseline survey. One-hour semi-structured interviews were completed with ten pregnant women and their spouses to assess content validity, content consistency, readability and comprehension, possible defects, and the time required to complete the questionnaire. The final questionnaire comprised five categories with a total of 10 items. Participants was informed by the three trained study staff and asked whether pregnant women or their spouses were willing to participate according to the order of patients’ admission to the hospital.

According to the requirement of establishing sample size of early questionnaire, the sample size should be at least 4 times of the number of questionnaire items,^{15,16} while some studies suggest that a sample size minimum was based on a subject to variable ratio of 5:1 and an optimal sample size based on a subject to variable ratio of 10:1.^{17,18} This questionnaire had 10 items, considering no response bias, and the sample size should be increased by 5%. Therefore, the ideal sample size = $10 * 10 * (1 + 5%) * 2 = 210$.

The questionnaire consisted of two sections: The first section surveyed demographic information, including age, occupation, education, urban or rural residence, religious affiliation, marital status, income, and health insurance status. The second section consisted of 10 open-ended questions were asked questions regarding drug clinical trials, whether they had heard of drug clinical trial, whether sick-pregnant woman should be medicated, and

whether it is necessary to develop drugs for pregnant women. They also answered the questions regarding financial compensation, risk awareness, psychological impact, and pregnancy outcomes.

Statistical Analysis

Data were analyzed by the SPSS statistical software (version SPSS 20.0, IBM SPSS Inc, Chicago, IL, USA). Count data are expressed as percentages (%), while measurement data are presented as mean \pm S.D. Comparison of means between groups was performed by an independent samples *t*-test or Mann–Whitney *U*-test. $\alpha = 0.05$ was the test level, $p \leq 0.05$ indicated statistically significant differences.

Results

Demographics of the Respondents

A total of 210 questionnaires were distributed to the study participants, 4 were excluded because they were incomplete, and 206 were finally included in the statistical analyses. Among them, 115 questionnaires had been completed by pregnant women while 91 questionnaires had been completed by their spouses. Of the 115 pregnant women, 10 had pregnancy complications, 63 had been admitted because of labor, while 42 had already delivered. There were no significant in age, educational level, insurance, previous birth, or income ($p > 0.05$). The percentage of full-time employed spouses (65.9%) was significantly

higher than that of part-time/non employed spouses (34.4%) (Table 1).

Attitudes of Pregnant Women and Their Spouses Regarding Participation in Clinical Trials

There were no significant differences between the proportions of pregnant women and their spouses, who had heard of clinical trials (50.43% vs 49.45%, respectively; $p > 0.05$). The proportions of pregnant women who thought drug clinical trials will increase the possibility of cure was significantly higher than that of their spouses ($p=0.001$). The majority of pregnant women and their spouses believed that medications should be used to treat illnesses during pregnancy. However, there were significant differences regarding whether it is necessary to develop drugs for pregnant women. Approximately 94.78% of pregnant women believed that there is a need to develop drugs for pregnant women, with only 16.48% of their spouses believing that it is necessary ($p=0.008$). Pregnant women exhibited similar views to those of their spouses and believed that drugs in clinical trials should be free, and that pregnant women who choose to participate in drug clinical trials should be more protected than others. Approximately 69.57% of pregnant women and 81.32% of their spouses did believe that participation in clinical trials will lead to discrimination against them and their

Table 1 Demographic Characteristic of Study Participants

Characteristic	Classification	Pregnant Women(%) <i>(n=115)</i>	Husband(%) <i>(n=91)</i>	p-value
Age (year)	<35	102 (88.7)	76 (83.5)	0.383
	≥ 35	13 (11.3)	15 (16.5)	
Educational level	Less than high school	21 (18.3)	18 (19.8)	0.940
	High school or more	94 (69.6)	73 (69.2)	
Employment	Full time	56 (49.6)	60 (65.9)	0.032
	Part time/not employed	59 (51.3)	31 (34.4)	
Insurance	Uninsured	8 (7.0)	12 (13.2)	0.147
	Maternity insurance/Medicare/Medicaid	107 (93.0)	79 (86.8)	
Previous birth	No	41 (35.7)	28 (30.8)	0.556
	≥ 1	74 (64.3)	63 (69.2)	
Income (per month)	<10,00 RMB	3 (2.61)	3 (3.30)	0.196 ^a
	10,00–50,00 RMB	18 (15.65)	10 (10.99)	
	>5000 RMB	94 (81.74)	78 (85.72)	

Notes: p-values of educational level, employment, employment, previous birth were obtained from Mann–Whitney *U*-test; p-values of age and income were obtained from independent sample *t*-test; ^aIncome per month ≤ 5000 RMB vs >5000 RMB.

offsprings while 93.04% of pregnant women and 91.21% of their spouses did not believe in terminating pregnancy in order to participate in drug clinical trials ($p=0.625$; Table 2).

Effects of Pregnancy History on Willingness to Participate in Clinical Trials

Most of the perspectives for women without a history of pregnancy and their spouses and those with a history of pregnancy and their spouses were not significantly different. However, there were significant differences perspectives regarding drugs development for pregnant women. The proportion of women without a history of pregnancy and their spouses who believed in the needs to develop drugs for pregnant women was significantly higher than when compared to those with a history of pregnancy and their spouses (100% vs 91.89%; 89.29% vs 80.95%; Table 3).

Effects of Employment on the Willingness of Pregnant Women to Participate in Clinical Trials

Most of the perspectives of full-time employed pregnant women and those part-time/non employed pregnant women were not significantly different. However, there were significant differences regarding whether drug clinical trials can increase the possibility of disease cure (98.21% vs 88.13%, $p=0.030$; Table 4).

Effects of Educational Levels of Pregnant Women's Spouses on Participation in Clinical Trials

Most of perspectives for spouses with different educational levels were not significantly different. However, there were significant differences in perspectives regarding whether financial compensation can motivate them to participate in clinical trials (Less than high school vs High school or more =77.78% vs 58.90%, $p=0.044$; Table 5).

Discussion

Ethical reasons preclude the inclusion of pregnant women in the vast majority of premarketing clinical trials for a long time,¹⁹⁻²¹ however, most women use more than one pharmaceutical drug during pregnancy that they did not use previously, in addition to vitamin/mineral supplements required during that time,^{22,23} but these pharmaceutical

drug is often based on limited scientific evidence insofar as the drug's safety and effectiveness are concerned. Indeed, most of the relevant studies were performed in non-pregnant women, so the data generated may not apply to pregnant women.²⁴ Given these considerations, pregnant women were excluded from previously drug clinical trials can be challenged.^{8,19,25}

As the policies and regulations about pregnant women including clinical trials were refined, many researchers focus to women's views about participating in clinical trials while pregnant.²⁶⁻²⁹ Several studies deemed pregnant women are unwilling to involving clinical trials because of women reluctance to exposing themselves and their fetus to a treatment that is still undergoing evaluation.^{30,31} Another study showed that the principal motivating factor in the decision to participate in a clinical trial was how well the study was explained by the recruiters, but the risk of unknown side effects was the principal barrier.³¹

A specific strength of our study is that we investigate the attitudes of the pregnant women and their spouses about participation in clinical trials, rather than just pregnant women. About 38% of survey respondents had heard of drug clinical trials, and 93.04% of pregnant women and 75.82% of their spouses believe that drug clinical trials could increase the possibility of disease cure. However, there were differences in opinion regarding whether it is necessary to develop drugs for pregnant women with 94.78% of pregnant women believing that they need to be developed, and only 16.48% of spouses believing that it is necessary. Therefore, pregnant women's spouses are more reluctant to include pregnant women in clinical trials than pregnant women. We suggest that when recruiting pregnant women into clinical trials, researchers should fully explain the clinical implications to their spouses so that pregnant women and their spouses can decide whether to participate. We did not obtain evidence supporting the reasons for pregnant women's spouses are more reluctant to include pregnant women in clinical trials than pregnant women, as there was no relevant literature to date, so we can only speculate what the reason for this is. Pregnant women have a longer contact with recruiters through daily prenatal testing compared with their spouses, so pregnant women are more profound in clinical trials. This observation is consistent with other studies showing that the principal motivating factor in the decision to participate in a clinical trial was how well the study was explained by the recruiters.³¹ Alternatively, or in addition, for pregnant

Table 2 Perspectives of Pregnant Women and Their Husbands

Question	Pregnant Women (%) (n=115)		Husband (%) (n=91)		p-value ^a
	Yes	No	Yes	No	
First category					
(1) Have you ever heard of a drug clinical trial?	58(50.43)	57(49.57)	45(49.45)	46(50.55)	0.888
(2) Do you think drug clinical trials can increase the possibility of disease cure?	107(93.04)	8(6.96)	69(75.82)	22(24.18)	0.001
Second category					
(1) Do you think it is necessary to use drugs when you are sick during pregnancy?	108(93.91)	7(6.09)	78(85.71)	13(14.29)	0.048
(2) Do you think it is necessary to develop drugs for pregnant women?	109(94.78)	6(5.22)	15(16.48)	76(83.52)	0.008
Third category					
(1) Do you have any concerns about drugs provided for free in clinical trials?	86(74.78)	29(25.22)	57(62.64)	34(37.36)	0.06
(2) Do you think financial compensation will motivate you to participate in clinical trials?	83(72.17)	32(27.83)	57(62.64)	34(38.20)	0.116
Fourth category					
(1) Do you think that it is more risky for pregnant women to participate in drug clinical trials when compared to others?	107(93.04)	8(6.96)	80(87.91)	11(12.09)	0.206
(2) Do you think that pregnant women who participate in drug clinical trials should be more protected for safety than others?	83(72.17)	32(27.83)	55(60.44)	36(39.56)	0.075
Fifth category					
(1) Do you think pregnant women's participation in clinical trials will lead to discrimination against themselves and/or their offsprings?	35(30.43)	80(69.57)	17(18.68)	74(81.32)	0.054
(2) Will you have the idea of terminating a pregnancy because of participating in drug clinical trials?	8(6.96)	107(93.04)	8(8.79)	83(91.21)	0.625

Note: ^aStatistical differences in views between pregnant women and their husbands regarding drug clinical trials for pregnant women.

Table 3 Perspectives of Pregnant and Their Husbands with Different Pregnancy Histories

Question	No Pregnancy History				p-value ^a	Times of Pregnancy ≥ 1				p-value ^a	p-value ^b
	Pregnant Women (%) (n=41)		Husband (%) (n=28)			Pregnant Women (%) (n=74)		Husband (%) (n=63)			
	Yes	No	Yes	No		Yes	No	Yes	No		
First category											
(1) Have you ever heard of a drug clinical trial?	16(39.02)	25(60.98)	13(46.43)	15(53.57)	0.541	42(56.76)	32(43.24)	32(50.79)	31(49.21)	0.485	0.104
(2) Do you think drug clinical trials can increase the possibility of disease cure?	40(97.56)	1(2.44)	20(71.43)	8(28.57)	0.002	67(90.54)	7(9.46)	49(77.78)	14(22.22)	0.039	0.661
Second category											
(1) Do you think it is necessary to use drugs when you are sick during pregnancy?	40(97.56)	1(2.44)	25(89.29)	3(10.71)	0.149	68(91.89)	6(8.11)	53(84.13)	10(15.87)	0.158	0.178
(2) Do you think it is necessary to develop drugs for pregnant women?	41(100.0)	0(0.00)	25(89.29)	3(10.71)	0.032	68(91.89)	6(8.11)	51(80.95)	12(19.05)	0.059	0.049
Third category											
(1) Do you have any concerns about drugs provided for free in clinical trials?	32(78.05)	9(21.95)	18(64.29)	10(35.71)	0.209	54(72.97)	20(27.03)	39(61.90)	24(38.10)	0.167	0.501
(2) Do you think financial compensation will motivate you to participate in clinical trials?	33(80.49)	8(19.51)	18(66.67)	9(33.33)	0.198	50(67.57)	24(32.43)	38(60.32)	25(40.32)	0.34	0.112
Fourth category											
(1) Do you think that it is more risky for pregnant women to participate in drug clinical trials when compared to others?	40(97.56)	1(2.44)	27(96.43)	1(3.57)	0.783	67(90.54)	7(9.46)	53(84.13)	10(15.87)	0.256	0.026
(2) Do you think that pregnant women who participate in drug clinical trials should be more protected for safety than others?	33(80.49)	8(19.51)	17(60.71)	11(39.29)	0.071	50(67.57)	24(32.43)	38(60.32)	25(39.68)	0.378	0.236
Fifth category											
(1) Do you think pregnant women's participation in clinical trials will lead to discrimination against themselves and/or their offsprings?	11(26.83)	30(73.17)	5(17.86)	23(82.14)	0.386	24(32.43)	50(67.57)	12(19.05)	51(80.95)	0.076	0.63
(2) Will you have the idea of terminating pregnancy because of participating in drug clinical trials?	1(2.44)	40(97.56)	3(10.71)	25(89.29)	0.149	67(90.54)	7(9.46)	58(92.06)	5(7.94)	0.753	0.453

Notes: ^aStatistical difference between pregnant women and their spouses; ^bStatistical different pregnant history of pregnant and their spouses regarding the attitudes of drug clinical trials for pregnant women.

Table 4 Views of Pregnant Women with Different Employment

Question	Full-Time Pregnant Women (%) (n=56)		Part-Time/Not Employed Pregnant Women (%) (n=59)		p-value
	Yes	No	Yes	No	
First category					
(1) Have you ever heard of a drug clinical trial?	30(53.57)	26(46.43)	27(47.76)	32(54.23)	0.51
(2) Do you think drug clinical trials could increase the possibility of disease cure?	55(98.21)	1(1.79)	52(88.13)	7(12.28)	0.03
Second category					
(1) Do you think it is necessary to use drugs when you are sick during pregnancy?	53(94.64)	3(5.36)	55(93.22)	4(7.02)	0.714
(2) Do you think it is necessary to develop drugs for pregnant women?	55(98.21)	1(1.79)	54(91.53)	5(8.77)	0.098
Third category					
(1) Do you have any concerns about drugs provided for free in clinical trials?	46(82.14)	10(17.86)	41(69.49)	18(31.58)	0.091
(2) Do you think financial compensation will motivate you to participate in clinical trials?	40(71.43)	16(28.57)	43(72.89)	16(27.11)	0.953
Fourth category					
(1) Do you think that it is more risky for pregnant women to participate in drug clinical trials when compared to others?	53(94.64)	3(5.36)	54(91.53)	5(8.47)	0.497
(2) Do you think that pregnant women who participate in drug clinical trials should be more protected for safety than others?	40(71.43)	16(28.57)	43(72.88)	16(27.11)	0.953
Fifth category					
(1) Do you think pregnant women's participation in clinical trials will lead to discrimination against themselves and/or their offsprings?	15(26.78)	41(73.21)	19(32.21)	40(67.79)	0.448
(2) Will you have the idea of terminating pregnancy because of participating in drug clinical trials?	3(5.36)	53(94.64)	5(8.47)	54(91.53)	0.497

Table 5 Views of Spouses with Different Educational Levels

Question	Less Than High School (%) (n= 18)		High School or More (%) (n= 73)		p-value
	Yes	No	Yes	No	
First category					
(1) Have you ever heard of a drug clinical trial?	10(55.56)	8(44.44)	35(47.95)	38(52.05)	0.604
(2) Do you think drug clinical trials could increase the possibility of disease cure?	11(61.11)	7(38.89)	25(34.25)	48(65.75)	0.07
Second category					
(1) Do you think it is necessary to use drugs when you are sick during pregnancy?	14(77.78)	4(22.22)	64(87.67)	9(12.33)	0.274
(2) Do you think it is necessary to develop drugs for pregnant women?	13(72.22)	5(27.78)	63(86.30)	10(13.70)	0.161
Third category					
(1) Do you have any concerns about drugs provided for free in clinical trials?	12(66.67)	6(33.33)	45(61.64)	28(38.36)	0.778
(2) Do you think financial compensation will motivate you to participate in clinical trials?	14(77.78)	4(22.22)	43(58.90)	30(41.10)	0.044
Fourth category					
(1) Do you think that it is more risky for pregnant women to participate in drug clinical trials when compared to others?	15(83.33)	3(16.67)	65(89.04)	8(10.96)	0.416
(2) Do you think that pregnant women who participate in drug clinical trials should be more protected for safety than others?	9(50.00)	9(50.00)	29(39.73)	44(60.27)	0.578
Fifth category					
(1) Do you think pregnant women's participation in clinical trials will lead to discrimination against themselves and/or their offsprings?	4(22.22)	14(77.78)	13(17.80)	60(82.91)	0.722
(2) Will you have the idea of terminating pregnancy because of participating in drug clinical trials?	2(11.11)	16(88.89)	6(8.22)	67(91.78)	0.569

women, it is possible that they were more worried about abortion or fear of reexposure to pregnancy.

Regarding medication costs in clinical trials, pregnant women and their spouses agree that clinical trials should be free. However, 72.17% of pregnant women and 62.64% of spouses believe that financial compensation will motivate them to participate in clinical trials. A global survey of registered clinical trials of pharmacological interventions in pregnancy conducted in 2016 showed that just 0.32% of all active registered studies were pregnancy drug trials (PDTs). The majority of PDTs focused on anesthesia/analgesia, preterm birth/tocolysis, labor induction, endocrine, and hypertensive disorders. Pharmaceutical companies fund only 7% of PDTs.³² Governments and charitable funds should increase their support for PDTs. The government should introduce relevant incentive policies to support pharmaceutical companies to invest in PDTs. Sheffield believes³³ that pharmaceutical industries and researchers are reluctant to research on pregnant women because of ethical considerations or fear that the lack of legislative authorization or incentives for such high-risk research will bring risks to pregnant women and fetuses. Therefore, there is an urgent need to improve of PDTs regulations.

The proportion of women without a history of pregnancy and their spouses who believed that it is necessary to develop drugs for pregnant women was significantly higher than that of women with pregnancy history and their spouses. In-depth studies should be performed to determine whether this outcome is attributed to the small sample size or whether pregnant women without a history of pregnancy and their spouses are more worried about the drug's safety or other reasons.

Different educational levels for the spouses of pregnant women were significant differences in whether financial compensation will motivate them to participate in clinical trials. The average annual income for spouses with less than high school education was 97,600 yuan and 157,800 yuan for those with a high school education or more. Therefore, we postulate that income differences are attributable to the above-mentioned differences. We are conscious that the questionnaire of clinical experiments should not involve economic motivations, but the purpose of this study to investigate whether participants with different income levels and different insurance conditions have different perspectives.

Conclusion

Due to concerns about the fetus, it is common for pregnant women to be reluctant to be included in clinical trials. However, pregnant women and their spouses agree that medical treatment should be given for illnesses during pregnancy, and clinical trials of drugs during pregnancy should be performed. This practice paradoxically increases the risk of fetuses using untested or sub-therapeutic drug regimens in clinical practice, especially the idea of their spouses. When recruiting pregnant volunteers for clinical trials, researchers should conduct in-depth consultations and education on drug clinical trials for pregnant women and their families and give a comprehensive introduction to trial drugs, to reduce the prejudice of pregnant women and their families for clinical trials.

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Disclosure

The authors report no conflicts of interest in this work.

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