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## Observational Study

**Birth experience of fathers in the setting of teenage pregnancy: Are they prepared?**

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**Author contributions:** Quinlivan JA and Petersen RW undertook concept and design, ethics approvals and established the study; Ngweso S undertook data acquisition and undertook the first draft of the manuscript; Quinlivan JA performed primary analysis; all authors interpreted the data and critically reviewed and subsequently approved the final manuscript for submission.

**Institutional review board statement:** The trial received institutional human ethics committee approval (Joondalup Health Campus Human Ethics Committee Number 1301).

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**Abstract****AIM**

To explore the birth experiences of teenage fathers and determine the extent to which they are prepared for childbirth.

**METHODS**

A mixed methods observational study was undertaken comparing the birth experience of 50 fathers in the setting of teenage pregnancy (teenage) compared to a group of 50 older fathers. Fathers were recruited in the antenatal period and completed structured questionnaires following the birth of their child. Quantitative and qualitative analysis was undertaken.

**RESULTS**

Teenage fathers were younger, less educated and less likely to attend prenatal childbirth education classes ( $P < 0.0001$ ). During birth, they were less prepared and consulted by attending staff (both  $P < 0.05$ ). They reported limited roles in intrapartum decision-making ( $< 20\%$ ). In multivariate analysis being a father in the setting of teenage pregnancy remained significantly associated with feeling unprepared for birth. The major themes in qualitative analysis were feeling unprepared,

shock, fear, a sense of detachment, happiness, pride, love of the baby and satisfaction with fertility.

### CONCLUSION

Teenage fathers are less prepared for the birth of their child and this results in shock, fear and detachment that may impact on the early father-infant relationship.

**Key words:** Fathers; Preparation for childbirth; Teenage fathers; Teenage pregnancy; Childbirth education; Birth

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**Core tip:** Fathers play an important role in their children's lives. However, few fathers in the setting of teenage pregnancy are prepared for the birth of their baby. They are less likely to attend childbirth preparation classes. Childbirth attendants do not engage them in intrapartum decision-making. Engaging fathers in the setting of teenage pregnancy in childbirth education and birth might reduce adverse feelings of shock, fear and detachment that might otherwise harm the early father-child attachment relationship.

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## INTRODUCTION

The birth of a child is a significant event in the human lifespan. This important milestone can have a profound impact upon the psychosocial functioning of the parents, the infant-parent relationship and the infants' development<sup>[1,2]</sup>. The impact of a negative childbirth experience has been associated with less maternal affection towards the baby, difficulty in breastfeeding, difficulty in adjusting to the role of motherhood and fear of having another birth<sup>[3]</sup>. Whilst difficult to objectify, determinants of childbirth satisfaction and the birth experience include expectations about birth, pain in labour, control of birth processes and levels of support from partners<sup>[4]</sup>.

The early involvement of fathers with their offspring is linked to improved cognitive and socio-economic development of children<sup>[5]</sup>. Paternal involvement during pregnancy is associated with lower rates of adverse outcomes such as preterm birth, low birth weight and fetal growth restriction<sup>[6]</sup>. It has been proposed that the positive effect of paternal involvement on birth outcomes is a consequence of the impact that involved fathers have on positively influencing maternal behaviours and reducing maternal stress<sup>[6]</sup>. For example, pregnant women with supportive partners are more likely to receive early antenatal care and to reduce negative health

behaviours such as smoking<sup>[6]</sup>.

It has become increasingly common for expectant fathers to attend and participate in antenatal care and education and there is a greater emphasis for 21<sup>st</sup> century fathers to have an increased level of involvement in the day-to-day care of their children<sup>[7,8]</sup>. In the past few decades, it has become normal for fathers to be present throughout labour and the birth of their baby<sup>[2]</sup>. In Australia, over 90% of fathers attend the birth of their child<sup>[8]</sup>.

Studies addressing teenage pregnancy usually emphasise the role of the mother and significantly less data is available concerning fathers (Quinlivan and Condon<sup>[9]</sup>, 2005; Shah *et al.*<sup>[10]</sup>, 2014). Furthermore, research addressing teenage pregnancy primarily explores the impact teenage pregnancy has on the birth and ongoing development of the child rather than considering the situation from the parent's perspective<sup>[9,11-14]</sup>. There is limited research investigating the expectations and decision-making processes in fathers in the setting of teenage pregnancy<sup>[12-16]</sup>.

The aim of this study was to determine how fathers in the setting of teenage pregnancy experienced the birth of their child. The specific aim was to determine the extent to which they felt prepared for birth.

## MATERIALS AND METHODS

### Type of study and ethics approval

The Australian Father's Study is a longitudinal study addressing father's attitudes towards antenatal, birth and postnatal care. The Australian Father's Study has institutional ethics committee approval (Joondalup Health Campus Human Ethics Committee). The trial is registered at the Australian and New Zealand Clinical Trials Registry (ACTRN 12613001273774). Individual informed consent was obtained from each participant. The Australian Father's Study includes a representative sample of Australian fathers as well as selected sampling of fathers in particular pregnancy settings.

### Study population

This manuscript reports on outcomes of fathers in the setting of teenage pregnancy (Teenage group fathers) and compares their outcomes to those of fathers recruited from the same area health network who were representative of the wider population of Australian fathers in terms of age, religious belief, years of education, employment and first time fatherhood status (Comparison fathers).

Of note, not all teenage group fathers were teenagers. The mean age of fathers in the setting of teenage pregnancy was 2.1 years older than the expectant teenage mother. By example, the partners of nineteen-year-old pregnant women were usually in their early twenties.

All fathers were recruited by research staff and completed questionnaires addressing demographic variables,

**Table 1 Demographics of fathers in the setting of teenage pregnancy compared to control**

	Teenage (n = 50)	Control (n = 50)	P-value
Age, mean (SD)	21.2 (1.2)	31.7 (3.1)	< 0.0001
Country of birth			
Australia	92%	65%	< 0.0001
Elsewhere	8%	35%	
Aboriginal or Torres Strait Islander	18%	3%	0.01
Relationship status			
Living with partner	32%	88%	< 0.0001
Not living with partner	68%	12%	
Education			
< 12 yr	24%	8%	< 0.0001
12 yr	74%	44%	
> 12 yr	2%	48%	
Employment			
No	32%	6%	< 0.0001
Yes-locally	54%	76%	
Yes-FIFO	14%	18%	
Hours employed			
0-15	35%	10%	< 0.0001
15-40	61%	12%	
40+	4%	78%	
Smoker	38%	20%	0.0087
First time father	96%	52%	< 0.0001
Pregnancy planning			
Natural - planned	22%	68%	< 0.0001
IVF - planned	0%	10%	
Unplanned	78%	22%	
Childbirth education class			
Full class	20%	52%	< 0.0001
Partial class	24%	8%	
Did not attend	56%	40%	

FIFO: Fly in, fly out worker; IVF: *In-vitro* fertilization.

attitudes and roles in decision-making. Quantitative and qualitative data was extracted from completed questionnaires.

### **Inclusion and exclusion criteria**

Expectant fathers were recruited *via* the pregnant mother, so the study was only able to include men where the mother acknowledged the man to be the father of the baby and gave consent for the father to participate. Fathers in the setting where pregnancy was complicated by a known fetal anomaly were excluded. Fathers with insufficient English to complete questionnaires were also excluded.

### **Variables to be measured and examined**

The birth questionnaire was completed within seven days of birth. It consisted of qualitative and quantitative components. The variables measured and examined through the questionnaire were collected in five broad areas: Background demographics, birth outcomes, engagement, involvement in decision making and overall birth experience. These variables were used as a framework for analysis of the primary outcome.

### **Primary hypothesis and sample size**

The primary hypothesis was that teenage group fathers

would feel less prepared for the birth of their baby than the comparison group fathers. Assuming 30% of teenage group fathers would feel prepared for birth, compared to 50% of comparison group fathers, a sample of 45 teenage group fathers provided 80% power with an error of 0.05 to detect this difference. The study recruited 50 teenage group fathers to ensure a sufficient sample, assuming incomplete data might be available from some questionnaires.

### **Statistical analysis**

Data was entered onto a dataset using Minitab® (version 16, University of Melbourne). A descriptive analysis was used for the quantitative data. In order to analyse for differences in responses between teenage group fathers and comparison group fathers, the significance (*P*) of the differences was determined by a  $\chi^2$  test for independence. Fisher Exact test was utilized where cell size was less than five. A *P*-value of 0.05 was set for rejection of the null hypothesis. A student *t*-test was used to compare continuous data.

For the qualitative data in the comments section of the questionnaire, an inductive content analysis was performed in accordance with methodology described by Elo and Kyngäs<sup>[17]</sup>. The written comments were independently read by the principal researchers and an abstraction process used to summarize and conceptualize the overall meaning and implications of the comments. Open coding was performed to maximize the number of headings in order to describe all aspects of the content. Both quantitative and qualitative aspects of the data were integrated for data interpretation.

## **RESULTS**

The demographic characteristics of the study participants are summarised in Table 1. Teenage group fathers were significantly younger ( $P < 0.0001$ ), more likely to have been born in Australia ( $P < 0.0001$ ) and be Aboriginal or Torres Strait Islander ( $P = 0.01$ ). Teenage group fathers were less likely to be living with the mother of the baby at the time of the birth ( $P < 0.0001$ ). They were less likely to have completed post-secondary education ( $P < 0.0001$ ). Whilst this may have been due to fewer opportunities due to their younger age, they had significantly higher rates of failing to complete secondary education compared to comparison fathers.

Teenage group fathers were more likely to be unemployed, and those who were employed were more likely to be employed part-time for less than 15 h a week ( $P < 0.0001$ ). Teenage group fathers were more likely to smoke ( $P = 0.0087$ ) and be a first time father ( $P < 0.0001$ ).

The teenage group fathers were significantly more likely to report that the pregnancy was unplanned ( $P < 0.0001$ ). They were also less likely to fully attend antenatal classes, even though there were more first time fathers in the teenage group ( $P < 0.0001$ ).

Table 2 summarises the role of fathers in relation to

**Table 2** Role of fathers in the setting of teenage pregnancy in intrapartum decision making

Did you play a role in the following decisions	Teenage (n = 50)	Control (n = 50)	P-value
Pain relief in labour			
Yes	3 (6%)	15 (30%)	0.0002
No	47 (94%)	35 (70%)	
Electronic foetal heart rate monitoring			
Yes	1 (2%)	8 (16%)	0.0069
No	49 (98%)	42 (84%)	
Artificial rupture of the membranes			
Yes	0 (0%)	4 (8%)	0.049
No	50 (100%)	46 (92%)	
Oxytocic infusion to accelerate labour			
Yes	0 (0%)	8 (16%)	0.0058
No	50 (100%)	42 (84%)	
Type of birth (by example need for assisted delivery or caesarean section)			
Yes	2 (4%)	14 (28%)	0.0002
No	48 (96%)	36 (72%)	
Who enters the delivery room			
Yes	9 (18%)	39 (78%)	< 0.0001
No	41 (82%)	11 (22%)	
Who held your baby immediately after the birth			
Yes	8 (16%)	40 (80%)	< 0.0001
No	42 (84%)	10 (20%)	
Timing of the baby's first feed			
Yes	2 (4%)	5 (10%)	0.16
No	48 (96%)	45 (90%)	

intrapartum decision-making. Teenage group fathers were less likely to play a role in the decision for the mother to have pain relief during labour ( $P = 0.0002$ ), electronic foetal heart rate monitoring ( $P = 0.0069$ ), undergo an artificial rupture of membranes ( $P = 0.049$ ) or an oxytocic infusion to accelerate labour ( $P = 0.0058$ ). Teenage group fathers were also less likely to play a role in deciding whether the mother should undergo an assisted vaginal delivery or Caesarean section ( $P = 0.0002$ ) and reported less of a role in decisions regarding who enters the delivery room ( $P \leq 0.0001$ ) and who held the baby immediately following birth ( $P < 0.0001$ ).

There was no statistically significant difference between the teenage group fathers and control as to decisions regarding the timing of the baby's first feed ( $P = 0.16$ ).

Results comparing the birth outcomes and experiences of fathers have been summarised in Table 3. There was no statistically significant difference between teenage group fathers and control fathers in regards to the gestational age of baby ( $P = 0.15$ ), gender of baby ( $P = 0.57$ ) and attendance of the father at birth ( $P = 0.60$ ).

Spontaneous delivery was higher and necessity for induction of labour lower with teenage group fathers as compared with the control group ( $P = 0.0007$  and  $P = 0.02$  respectively). However, a higher proportion of teenage group babies were born with birth weights below 10% adjusted for gestational age ( $P = 0.037$ ) and more teenage group babies required admission to a neonatal nursery ( $P = 0.018$ ).

A significant proportion of teenage group fathers felt

**Table 3** Birth outcomes and experiences of fathers in the setting of teenage pregnancy

Birth outcomes	Teenage (n = 50)	Control (n = 50)	P-value
Gestational age of baby			
Preterm (< 37 wk)	6 (12%)	4 (8%)	0.15
Term (37-41 wk)	42 (84%)	41 (82%)	
Post term (> 41 wk)	2 (4%)	5 (10%)	
Induction of labour			
Yes	9 (18%)	14 (28%)	0.02
No	40 (80%)	31 (62%)	
N/A (had elective CS)	1 (2%)	5 (10%)	
Newborn gender			
Male	25 (50%)	27 (54%)	0.57
Female	25 (50%)	23 (46%)	
Birth weight below 10% adjusted for gestational age			
Yes	8 (16%)	4 (8%)	0.037
No	42 (84%)	46 (92%)	
Delivery mode			
Spontaneous vaginal birth	39 (78%)	26 (52%)	0.0007
Assisted vaginal birth	6 (12%)	8 (16%)	
Elective Caesarean birth	1 (2%)	5 (10%)	
Non-elective Caesarean birth	4 (8%)	11 (22%)	
Required admission to a neonatal nursery			
Yes	10 (20%)	5 (10%)	0.018
No	40 (80%)	45 (90%)	
Father attended the birth			
Yes	49 (98%)	50 (100%)	0.91
No	1 (2%)	0 (0%)	
Father felt prepared for the birth			
Yes	6 (12%)	42 (84%)	< 0.0001
Neutral	37 (74%)	2 (4%)	
No	7 (14%)	4 (8%)	
Father found midwifery staff to be helpful			
Yes	40 (80%)	41 (82%)	0.60
Neutral	8 (16%)	6 (12%)	
No	2 (4%)	3 (6%)	
Father found medical staff to be helpful			
Yes	38 (76%)	41 (82%)	0.004
Neutral	10 (20%)	4 (8%)	
No	2 (4%)	5 (10%)	
Father felt consulted by staff during birth			
Yes	5 (10%)	40 (80%)	< 0.0001
Neutral	22 (44%)	6 (12%)	
No	23 (46%)	4 (8%)	

N/A: Not applicable.

both ill-prepared for the birth of their child and felt a lack of consultation by staff during the birthing process (both  $P < 0.0001$ ).

In multivariate analysis, after adjusting for other variables significant at a univariate level of  $P < 0.1$  as being significant associations of not feeling prepared for birth (age, relationship status, employment, pregnancy planning, childbirth education class, delivery mode, and admission to neonatal nursery), teenage group fathers remained a significant independent association ( $P = 0.0008$ ).

It was not the aim, nor was the study adequately powered, to detect a difference between fathers who were teenagers (aged less than 20 years) compared to those who were older but within the context of a maternal teenage pregnancy. However, no significant

differences in key outcomes under evaluation were detected between these groups (all  $P > 0.05$ ).

### Qualitative analysis

Thirty of the 50 teenage group fathers wrote comments about the birth experience. Four positive and four negative themes were identified.

The first positive theme was happiness. Twenty fathers wrote comments relating to their general sense of happiness. Fathers said: "this is the best experience of my life"; "I'm so happy. I've been jumping around".

The second positive theme was love for the baby. Fifteen fathers wrote comments about love for their baby. Fathers called their baby "precious", "amazing", "wonderful", and many used the word "love" to express their feelings. By example fathers stated: "she is the most precious (sic) thing I have"; "It was amazing how I just suddenly love her".

The third positive theme was pride and a sense of achievement. Seven respondents wrote comments related to this theme. Fathers stated: "...I've really achieved something"; "the best thing I've ever done".

Despite being young, six fathers expressed satisfaction with their fertility as the final theme. One father said: "it's nice to know I'm not firing blanks".

There were four negative themes. The first negative theme related to fathers feeling unprepared for the birth process. A total of 19 fathers expressed this theme. Comments included: "It was pretty fast and furious. I wasn't prepared"; "much more gory than I thought it would be"; "Horrible really. I wasn't ready for that".

The theme of shock was expressed by seven fathers. Comments included: "I'm in shock"; "My heart raced and I was shaking"; "Terrifying". Fear for the baby was the third negative theme. Five fathers expressed a fear that their baby might die or be injured or disabled. Comments included: "...frightened (sic) he would die"; "when that suction thing came out it freaked me out. I thought the baby was going to die or have its head torn off". The final theme was a sense of detachment from the birthing process. Four fathers made comments, including: "I felt like I was watching a TV program"; "it felt like it was happening to someone else and not me". Interestingly, no fathers wrote comments about the mother of the baby, or any other relatives or in relation to care providers. All comments related to either the father and/or the baby.

## DISCUSSION

Research into the role and experiences of fathers during the birthing process is limited. This is one of the first studies specifically examining the birth experience of fathers in the setting of teenage pregnancy. The teenage group fathers reported feeling less prepared and less consulted during birth and had less participation in decision-making processes. These findings, together with the negative themes of being unprepared, shocked, fearful for the baby and having a sense of detachment,

support the study hypothesis that fathers in the setting of teenage pregnancy are less prepared and engaged in birth than other fathers.

Teenage group fathers were more likely to be having their first baby. We considered this might explain the higher rates of feeling unprepared and shocked at the birthing process. However, in multivariate analysis, first time fatherhood status was not significantly associated with feeling unprepared for the birth and teenage group fatherhood remained significant.

One strategy to help teenage group fathers prepare for birth would be through participation in childbirth education classes. However, teenage group fathers were less likely to attend such classes, even though they were more likely to be a first time father. The classes were free of charge, so there was no cost disincentive to attendance. Teenage group fathers were more likely to be unemployed or employed only part time, so time constraints were also unlikely to be a barrier to attendance. It may be that teenage group fathers felt reluctant to attend childbirth education classes due to their age. This area requires further exploration in a directed qualitative study.

The educational and employment differences between teenage group fathers and comparison fathers may impact upon the resources these fathers have to assist the mothers with emotional support in labour and subsequent parenting. The quality of support material provided to fathers is associated with children's outcomes. The social disadvantage of younger fathers has been explored by Mollborn and Lovegrove<sup>[15]</sup>, who considered the lower income and education of teenage fathers to pose a "contextual risk" for their children. The degree of social disadvantage experienced by teenage fathers is likely a significant contributing factor to the degree of unpreparedness and reduced level of satisfaction with the birth process<sup>[14]</sup>. There is a likely association between teenage pregnancy and factors consistent with social disadvantage including poverty, unemployment, poor academic achievement and physical abuse<sup>[16]</sup>.

Sixty-eight percent of teenage group fathers were not living with the mother as compared with 12% of control group fathers and 96% of the teenage group fathers were first time parents. These social factors provide plausible explanation as to why the teenage group fathers reported a limited role in intrapartum decision-making (all decisions < 20% identified a role). It could be expected that a father who is not living with the mother of the baby would be expected by care providers and the father himself, to have less say in intrapartum decision-making processes. Similarly, a first time father may feel more comfortable deferring decisions to the mother, the mother's immediate family (e.g., future grandmother) or as directed by attending medical and/or midwifery staff.

The majority of teenage group fathers reported the pregnancy was unplanned. This lack of control over planning may also have impacted upon father's experiences of feeling engaged in intrapartum decision-making and birth. Expectant fathers decision-making in the setting of

teenage pregnancy is complex and underlying personality traits, idealisation of pregnancy and relationship quality may impact upon levels of comfort and engagement with the expectation of fatherhood<sup>[12-14]</sup>.

As described, thematic analysis of qualitative comments from the teenage group fathers revealed four main negative themes; unpreparedness, shock, fear and a sense of detachment from the birth. Previous research has shown similar themes. Deave and Johnson<sup>[2]</sup> conducted a series of semi-structured interviews amongst first-time fathers and identified themes of apprehension, unpreparedness, fear, anxiety and the feeling of being a helpless bystander. Given partner support is a key feature to successful outcomes in teenage pregnancy, it is important father's fears and lack of preparedness for birth are resolved<sup>[10]</sup>.

There were a number of limitations to this research. All fathers who participated in the questionnaire were recruited *via* women attending antenatal clinics who consented to the researchers approaching the father. We were therefore not able to secure input from men estranged from their partner. Similarly, fathers where pregnancy was complicated by a known fetal anomaly or where they lacked sufficient English to complete questionnaires, were excluded. Finally, fathers in the teenage group were not necessarily teenagers, with the mean age of fathers 2.1 years older than the pregnant mother.

### Implications for practice

Fathers play an important role in the lives of their children. Few fathers in the setting of teenage pregnancy are prepared for the birth of their baby. They are not engaged in intrapartum decision-making and do not feel consulted by attending staff. They are less likely to attend childbirth preparation classes. Engaging fathers in the setting of teenage pregnancy in childbirth preparation might reduce adverse feelings of shock, fear and detachment associated with their child's birth. This may facilitate early father-infant attachment in this vulnerable group.

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## COMMENTS

### Background

Research on the attitudes of fathers in the setting of teenage pregnancy is limited.

### Research frontiers

Engaged fathers in the setting of teenage pregnancy improves pregnancy, birth and mother and child postnatal outcomes. To improve engagement, the authors

first need to understand why such fathers may not be engaged with birth processes.

### Innovations and breakthroughs

Current processes leave teenage fathers unprepared for the birth of their child and this promotes disengagement. Greater antenatal engagement may overcome this problem.

### Applications

This research is directly applicable to clinical staff who provide antenatal care for teenage mothers.

### Terminology

The term "fathers in the setting of teenage pregnancy" is a specific term that refers to the man who fathered the child when a teenage female is pregnant. Given fathers are on average, 2 years older than mothers, many fathers in this setting will not be teenagers themselves, but may be in their early twenties.

### Peer-review

This is a well written well designed study to evaluate paternal preparedness in adolescent pregnancies.

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## Retrospective Cohort Study

**Observed prevalence and risk factors of birth defects in Shanghai, China**

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Data sharing statement: The data used in the study may be requested from Ji-Mei Wang ([wjm8219@163.com](mailto:wjm8219@163.com)).

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**Abstract****AIM**

To investigate the prevalence and related risk factors of birth defects in Shanghai.

**METHODS**

This report describes a population-based study of all births at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China from January 2008 to December 2014. A logistic regression analysis was used to identify the parameters that are independently associated with birth defects.

**RESULTS**

A total of 82814 births, including 824 cases of birth defects, were recorded. The rate of birth defects was 0.995 per 100 births. In the multivariable regression analysis, neonatal birth defects were likely to be associated with higher gravidity [odds ratio (OR), 1.099, 95%CI: 1.024-1.178], premature birth (OR = 1.905, 95%CI: 1.501-2.418), low birth weight (OR = 3.844, 95%CI: 3.004-4.919), twin births or higher order multiple pregnancies (OR = 1.477, 95%CI: 1.107-1.969), cesarean delivery (OR = 1.184, 95%CI: 1.016-1.380) and registration as part of a migrant population (OR = 1.380, 95%CI: 1.167-1.632). Female infants were less likely to have birth defects than male infants (OR = 0.710, 95%CI: 0.616-0.818).

**CONCLUSION**

Higher gravidity, premature birth, lower birth weight,

twin births or higher order multiple pregnancies, and registration as part of a migrant population are independent predictors of birth defects.

**Key words:** Birth defects; Prevalence; Risk factors; Shanghai

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**Core tip:** We evaluated the prevalence and the related risk factors of birth defects in Shanghai. The ten most frequent birth defects in newborns each year were congenital heart defects, polydactyly and syndactyly, hypospadias, orofacial clefts, congenital ear malformation, Down syndrome, strephenopodia/strephexopodia, intestinal atresia/stenosis, chromosomal disorders, and kidney malformations. We also observed that higher gravidity, premature birth, lower birth weight, cesarean delivery, twin or multiple births and being a member of a migrant population are high risk factors of birth defects according to a large patient database.

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## INTRODUCTION

Birth defects are defined as structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life and that can be detected prenatally, at birth or later in life. As previously reported, birth defects, including congenital malformations (they form the exterior or microscopic structures within the abnormal fetus), mental retardation, and genetic chromosomal disorders, among others, are a major cause of pediatric morbidity and mortality and can occur in single or multiple organs<sup>[1,2]</sup>. Improvement of antenatal diagnosis and electronic medical record systems allows reliable population-based studies that focus on congenital anomalies.

In the 1980s, China implemented a birth defect surveillance system. Approximately 470 hospitals in 31 provinces, municipalities and autonomous regions in the nation participate in this monitoring network; this three-level monitoring network covers nearly 80 million people. Based on continuous dynamic monitoring, we obtained accurate and reliable data that were vital to the health of Chinese women and their children, and provided a scientific basis for decision-making regarding maternal and neonatal health in our country. Located in Eastern China, Shanghai is the most economically developed metropolitan area and has participated in birth defect surveillance since 1986. To ensure the

accuracy of the surveillance information, information was directly transferred through the Internet. The objective of this study is to estimate the temporal trend and epidemiologic characteristics of birth defects at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai from 2008 to 2014.

## MATERIALS AND METHODS

### Data sources and inclusion criteria

All the data in the investigation were obtained from the birth defect surveillance network of Obstetrics and Gynecology Hospital of Fudan University and were collected from 2008 to 2014. The anomalies were diagnosed prenatally, at birth or 7 d after delivery. According to the national hospital-based system that has been administered in China for more than 25 years, the birth population includes fetuses and neonates at 28 wk or more of gestation, including live births and still births, who are born in hospitals within the surveillance system<sup>[3,4]</sup>. According to the requirements of the Chinese Birth Defects Program, the screening of perinatal infants for birth defects was conducted by two pediatric specialists. An interview of the mothers was conducted, and the "birth defect registration card" was completed after the clinical examinations. Furthermore, the well-trained professionals of the Maternal and Neonatal Health Care Institute in the area of our hospital verified the information on a quarterly basis, reviewed the medical records that pertained to the prenatal diagnosis (sonography, genetic tests or pathology) and coded all congenital anomalies. An assessment of birth defects was made according to the Tenth Revision of International Classification of Diseases (ICD-10).

### Clinical investigations

Gastrointestinal malformations were diagnosed by gastrointestinal imaging or orthostatic abdominal film. Congenital heart defects (CHDs), kidney malformations, and hydrocephalus were assessed by ultrasonography during the fetal period and were confirmed after birth. Other birth defects, such as syndactyly, polydactyly, accessory auricle anomalies, orofacial clefts (OFCs), hypospadias and other visible birth defects were diagnosed based on the International Classification of Diseases (ICD-10). Prenatally diagnosed malformations were confirmed during the postnatal period before clinical symptoms were evident.

### Statistical analysis

In this study, data on the ten most frequent congenital malformations in patients from the database who registered during 2008-2014 were selected for analysis. Only isolated congenital malformations were included according to the International Classification of Diseases (ICD-10). The *t*-test, ANOVA and  $\chi^2$  test were employed where applicable. In addition, a multiple logistic re-

**Table 1** Ten most common birth defects and their prevalence rate at the Obstetrics and Gynecology Hospital of Fudan University, 2008-2014, *n* (%)

Birth defects	2008	2009	2010	2011	2012	2013	2014	Total (average prevalence)
Congenital heart disease	26 (0.394)	31 (0.470)	28 (0.286)	36 (0.280)	29 (0.196)	35 (0.232)	44 (0.470)	229 (0.277)
Polydactyly/syndactyly	17 (0.258)	27 (0.409)	21 (0.215)	35 (0.272)	36 (0.243)	41 (0.271)	41 (0.410)	218 (0.263)
Hypospadias	14 (0.212)	7 (0.106)	10 (0.102)	12 (0.093)	19 (0.128)	14 (0.093)	11 (0.106)	87 (0.105)
Orofacial clefts	4 (0.060)	11 (0.167)	13 (0.133)	5 (0.039)	14 (0.094)	15 (0.100)	17 (0.167)	79 (0.095)
Congenital ear malformations	3 (0.045)	9 (0.136)	17 (0.174)	13 (0.101)	6 (0.041)	6 (0.040)	5 (0.136)	59 (0.071)
Down syndrome	1 (0.015)	2 (0.030)	4 (0.041)	3 (0.023)	10 (0.067)	6 (0.040)	2 (0.030)	28 (0.034)
Strephenopodia/strephexopodia	1 (0.015)	5 (0.076)	9 (0.092)	3 (0.023)	2 (0.014)	3 (0.020)	1 (0.006)	24 (0.029)
intestinal atresia/stenosis	5 (0.076)	2 (0.030)	5 (0.051)	1 (0.008)	3 (0.020)	6 (0.040)	2 (0.012)	24 (0.029)
Chromosomal disease	5 (0.076)	0 (0)	1 (0.010)	1 (0.008)	0 (0)	5 (0.033)	4 (0.023)	15 (0.019)
kidney malformations	2 (0.030)	2 (0.030)	2 (0.020)	0 (0)	0 (0)	0 (0)	7 (0.041)	13 (0.016)
Number of births	6596	6602	9786	12844	14832	15110	17044	82814

gression analysis was performed to analyze the relationship between birth defects and potential risk factors. Confidence intervals were given, and a *P* value of < 0.05 was considered significant. All statistical analyses were conducted using SPSS version 13.0 (IBM Corp., Armonk, NY, United States).

## RESULTS

### Descriptive statistics

The mean age of women who were permanent residents at the time of childbirth was 29.05 ± 3.63 years of age, which was significantly higher than that of women in the migrant population (28.90 ± 4.54 years of age; *t* = 3.58, *P* < 0.001).

Of 824 cases with birth defects, 484 (58.7%) were male infants, 335 (40.7%) were female infants, and 5 (0.6%) were ambiguous in regard to sex. The male to female ratio was 1.44:1. Moreover, in the current study, 38236 cases (46.2%) were delivered vaginally, while the remainder (53.8%) were delivered by cesarean section. The average maternal age of women who underwent vaginal delivery was 28.42 ± 3.51 years, while that of women who underwent caesarean delivery was 29.55 ± 3.96 years (*t* = 43.62, *P* < 0.001). The frequency of cesarean sections increased with age ( $\chi^2 = 1607.30$ , *P* < 0.001).

### Ten most frequent birth defects and their prevalence

From 2008 to 2014, 82576 live births and 238 stillbirths were recorded. Of them, 824 infants with congenital malformations accounted for a prevalence of 0.995 per 100 births (824/82814). In this study, the incidence of multiple birth defects concurrently present in a neonate was 7.3% (60/824). Among these infants with multiple congenital anomalies (MCA), the co-occurrence of anomalies may have been due either to chance (*i.e.*, unrelated etiologies) or a pathogenically associated pattern of anomalies<sup>[5]</sup>. There were 42829 male infants (51.7%) and 39990 females (48.3%), and the overall ratio of male to female infants was 1.07:1.

The ten most frequent birth defects at the Obstetrics and Gynecology Hospital of Fudan University from

2008 to 2014 were listed according to the International Classification of Diseases (ICD-10). The three most frequent birth defects were CHDs (229), polydactyly or syndactyly (218) and hypospadias (87). The number of severe CHD cases declined annually. Cleft lip with palate, cleft lip alone and cleft palate alone accounted for 10 (2.7%), 16 (20.1%), and 53 (67.1%) of all OFC cases, respectively. Among the 218 perinatal cases of polydactyly/syndactyly, 152 occurred in the hands, 60 occurred in the feet, and 6 occurred in both (Table 1).

The ten most frequent birth defects of newborns annually were CHDs (0.277%), polydactyly and syndactyly (0.263%), hypospadias (0.105%), OFCs (0.095%), congenital ear malformations (0.071%), Down syndrome (0.034%), strephenopodia/strephexopodia (0.029%), intestinal atresia/stenosis (0.029%), chromosomal disorders (0.019%), and kidney malformations (0.016%). CHDs, intestinal atresia/stenosis, kidney malformations, hypospadias, OFCs, polydactyly and syndactyly, and accessory auricle anomalies have increased in the last six years, whereas the prevalence of Down syndrome has remained stable. Although the three major subtypes of neural tube defects (NTDs), namely, anencephaly, spina bifida, and encephalocele, were not among the ten most frequent birth defects, they have continued to decrease annually. In addition, congenital heart disease was the most frequent birth defect with a prevalence of 0.394% in 2008, 0.470% in 2009, 0.286% in 2010, 0.280% in 2011, and 0.470% in 2012. However, polydactyly/syndactyly had the highest prevalence in 2012 (0.243%) and 2013 (0.271%) (Table 1).

### Multiple logistic regression

To analyze the relationship between the occurrence of birth defects and potential risk factors, a multiple logistic regression model was applied. In this model, the variables were listed as follows: Maternal age (< 20, 20-24, 25-29, 30-34, 35-39, ≥ 40), parity (first, second, third, and fourth or more pregnancy), gestation (first, second, third, and fourth or more pregnancy), sex of the infant (male, female), gestational age (≥ 37 wk, < 37 wk), birth weight (normal, extremely low birth weight (ELBW), very low birth weight (VLBW) and low

**Table 2 Multiple logistic regression of risk factors for birth defects, 2008-2014**

Factors	Delivery	Cases (%)	OR (95%CI) Enter	P value
Maternal age (yr)				
< 20	274	2 (0.7)	1	-
20-	7353	82 (1.1)	1.951 (0.473, 8.045)	-
25-	41861	392 (0.9)	1.818 (0.446, 7.406)	-
30-	26285	249 (0.9)	1.686 (0.413, 6.886)	-
35-	6080	74 (1.2)	1.806 (0.435, 7.494)	-
40-	961	20 (2.1)	2.676 (0.611, 11.715)	-
Parity order	-	-	0.835 (0.687, 1.014)	0.069
Gravidity order	-	-	1.099 (1.024, 1.178)	0.009
Gender				
Male	42828	484 (1.1)	1	
Female	39986	335 (0.8)	0.710 (0.616, 0.818)	< 0.001
Gestational age (wk)				
≥ 37	75750	556 (0.7)	1	
28-37	7064	263 (3.7)	1.905 (1.501, 2.418)	< 0.001
Birth weight				
Normal	73133	536 (0.7)	1	
ELBW and VLBW and LBW	4742	242 (5.1)	3.844 (3.004, 4.919)	< 0.001
Macrosomia	4939	41 (0.8)	1.090 (0.790, 1.503)	0.601
Plurality				
Singletons	79440	691 (0.9)	1	
Twins or higher order multiple pregnancies	3374	128 (3.8)	1.477 (1.107, 1.969)	0.008
Household registration				
Permanent population	68930	617 (0.9)	1	
Migrant population	13884	202 (1.5)	1.380 (1.167, 1.632)	< 0.001
Delivery mode				
Vaginal delivery	38236	291 (0.8)	1	
Cesarean delivery	44578	528 (1.2)	1.184 (1.016, 1.380)	0.031

ELBW: Extremely low birth weight; VLBW: Very low birth weight; LBW: Low birth weight.

birth weight (LBW), macrosomia), number of fetuses (single, twins, and multiple births), delivery mode (vaginal delivery, cesarean delivery) and household registration (permanent population, migrant population). The analysis suggested that higher gravidity [odds ratio (OR) = 1.099, 95%CI: 1.024-1.178], premature birth (OR = 1.905, 95%CI: 1.501-2.418), low birth weight (OR = 3.844, 95%CI: 3.004-4.919), twins or multiple pregnancies (OR = 1.477, 95%CI: 1.107-1.969), cesarean delivery (OR = 1.184, 95%CI: 1.016-1.380) and registration as part of a migrant population (OR = 1.380, 95%CI: 1.167-1.632) were significantly associated with birth defects. Female infants were less likely to have birth defects (OR = 0.710, 95%CI: 0.616-0.818) (Table 2).

## DISCUSSION

Compared with previous reports, a larger sample analysis was used here to estimate the epidemiologic characteristics of birth defects, and a multivariate analysis was applied to explore the associations between possible risk factors and birth defects. The incidences of birth defects in Shanghai in 2011, 2012, 2013, were 1.17%, 1.05% and 0.98%, respectively, which are relatively lower than the national average prevalence (1.10-1.45 per 100 births)<sup>[2]</sup>. These results could be attributed to the salubrious climate, availability of rich and diverse fresh fruit, and more developed economic

and advanced health technologies, which benefitted the health of pregnant women and their fetuses in Shanghai. The rate of birth defects at our hospital was 0.995 per 100 births, which was in agreement with the overall rate in Shanghai<sup>[6]</sup>. The incidence of birth defects in eastern areas was higher than that in middle and western areas within China in 2014<sup>[6]</sup>. Pregnant women in Shanghai regularly participate in prenatal screenings and are likely to maintain the pregnancy unless serious diseases such as very severe heart defects and multiple malformations are present, which leads to fewer terminations of pregnancy in Shanghai than in other areas.

Birth defects have already become the primary cause of neonatal mortality and morbidity, and could also be an important source of distress for parents and families. Our hospital regularly monitors women with gestational diabetes and hypertensive disorders. Our hospital also focuses on screening for major malformations during the first trimester by ultrasound and the monitoring of fetal growth to find potential anomalies. Additionally, the use of invasive prenatal diagnostic techniques including amniocentesis, chorionic villus sampling (CVS), fetal blood sampling and embryoscopy, help in the identification of anomalies. Therefore, the Chinese government has abolished intervention using the three-step-prevention mode to improve the physical quality of newborns. With innovations in the quality and accessibility of diagnostic tests, increasing numbers of

birth defects are diagnosed<sup>[7]</sup>.

The prevalence of CHDs and polydactyly/syndactyly in Shanghai was 0.277 per 100 and 0.263 per 100, respectively, which was higher than the prevalence in Inner Mongolia (0.171 per 100 and 0.085 per 100, respectively)<sup>[8]</sup>. CHDs were the most frequent anomalies in our study, and their prevalence was lower in Shanghai than in all of China (32.74-43.22 per 10000 live births)<sup>[2]</sup>. According to previous reports, compared with other races, in Asians, CHDs ranked as the most frequent among general birth defects, with a higher incidence of pulmonary stenosis (PS) and tetralogy of Fallot (TOF), but a lower incidence of left-sided obstructions, transposition of the great arteries (TGA), and tricuspid atresia<sup>[9]</sup>. Since 2007, CHDs have been reported as the most frequent birth defects in China<sup>[2]</sup>. This might be attributed to the popularization of prenatal diagnosis and postpartum echocardiographic screening<sup>[2]</sup>. The prevalence of polydactyly/syndactyly, hypospadias, cleft lip and palate and accessory auricle anomalies was increased in our study. This may be due to environmental factors, IVF (*in vitro* fertilization) or ICSI (intracytoplasmic sperm injection). Since the time the first infant was born as a result of ART in China in 1988, more and more infants have been born after use of ART<sup>[10]</sup>. Compared with births after spontaneous conception, births resulting from IVF and ICSI combined were found to be associated with a significantly increased risk of any birth defect (unadjusted odds ratio, 1.43; 95%CI: 1.26-1.62)<sup>[11]</sup>. Moreover, anomalies of the limbs, face, and genitourinary system (34%) were found to be associated with the lowest detection rate by ultrasonography<sup>[12]</sup>, and thus polydactyly/syndactyly, hypospadias, cleft lip and palate, and accessory auricle anomalies were difficult to detect by prenatal screening and diagnostic methods.

Specifically, the earliest reports of NTDs (neural tube defects) in China showed an overall prevalence of 27.4 per 10000 in 1986 and 1987, while in our study, the prevalence was lower; therefore, NTDs were not among the 10 most common birth defects (0.01 per 100 individuals). Moreover, the rate of NTDs was also lower than that in Mongolia (0.201 per 100 individuals)<sup>[8]</sup>. This decrease is due to the nationwide availability of complementary folic acid supplements as of 2009<sup>[13,14]</sup> and prenatal ultrasound screening. Early interventions, such as induced abortion, would be performed if neural tube defects were detected by clinical and ultrasound tests.

In our study, the overall ratio of male to female infants with birth defects was 1.44:1. The incidence of birth defects in male infants was higher than that in female infants, which was consistent with national survey results<sup>[2,7]</sup>. Therefore, the birth defects in male infants may account for more in the whole population. This may be due to differences in hormone levels or because the Y chromosome has a higher susceptibility to damage than the X chromosome<sup>[15]</sup>. In addition,

external genital deformities in females were less likely to be found than those in males. However, earlier abortions of female fetuses may have affected the sex ratio. Combined with the one-child policy, the traditional preference for male infants in China has resulted in widespread abortions of female fetuses<sup>[16]</sup>.

The prevalence of birth defects in preterm infants was significantly higher than that in term infants, which paralleled what has been found in other populations. A possible explanation for this result might be that birth defects in premature infants were associated with maternal health, nutrition, older maternal age, hypertension, diabetes and drug use, among other factors, during pregnancy. Previous reports revealed that the most common birth defects were intestinal atresia, gastroschisis deformity, and esophageal atresia, especially in premature babies of gestational age 24 to 28 wk<sup>[17]</sup>.

The incidence of birth defects in newborns with low birth weight was much higher than that in those with normal birth weight or macrosomia, which was consistent with the results of a previous study. In recent years, the number of elderly parturient women (older than 35 years) has increased from 562 cases in 2008 to 1562 cases in 2014. In a previous study, gastroschisis, cleft lip and palate, Down syndrome and other chromosomal diseases were found to be associated with the age of the mothers, and older mothers were at a higher risk of premature labor and pregnancy complications<sup>[18]</sup>. Several studies found that maternal age < 20 or > 35 years was a risk factor for birth defects<sup>[8,19]</sup> because the eggs of women younger than 20 years were not fully mature, whereas ovarian function and egg quality in women older than 35 years were poor. However, the results of one study indicated that the increased risk related to maternal age was negligible, especially when compared with the occurrence of chromosomal abnormalities<sup>[20]</sup>. Nonchromosomal abnormalities are common in Europeans, and the lowest prevalence is observed in mothers aged between 30 and 34 years<sup>[21]</sup>. Advanced maternal age (over 35 years of age) was found to be related to a higher prevalence of birth defects, but no significant difference was found between these women and younger women<sup>[22]</sup>. Based on this result, antenatal care and prenatal screening should be directed to pregnant women over 35 years of age. Furthermore, with the promotion of "two children for one family", which has been the national policy since 2014, the proportion of older mothers is expected to increase; this in turn will bring great challenges to the prevention and treatment of birth defects.

The mean age of women who were permanent residents at the time of childbirth was significantly higher than that of women in the migrant population. Women in the migrant population came to Shanghai from other areas within six months before pregnancy. This population includes older mothers with pregnancy-

associated diseases and temporary workers. Therefore, we observed a higher risk of birth defects in the migrant population than in the permanent resident population, and several possible explanations for this are discussed below. First, living conditions and occupational exposure might be more serious for these women, and they may more easily encounter substances that may not be present in urban areas such as mercury, lead, inhalable particles, and organic solvents, which are related to birth defects. Previous reports indicated a correlation between maternal agricultural work and birth defects<sup>[23]</sup>. Second, most migrants, including factory workers, builders and those in other vulnerable occupations, might be less educated and unaware of the importance of maternal health<sup>[24]</sup>. The severe perinatal complications in most migrant women were possibly due to their temporary move to Shanghai in order to give birth at a tertiary center, rather than at a rural hospital, where it is safer for mothers and fetuses. Higher capabilities of healthcare personnel and better living environments contribute to improved maternal health knowledge scores, and thus more women with high-risk pregnancies were included in the migrant population<sup>[25]</sup>. Furthermore, migrant women and permanent residents may have different lifestyles, habits or nutrition supplements<sup>[8]</sup>. For example, the benefits of multi-vitamin supplements during pregnancy may be insufficiently promoted among migrant populations. A previous study showed that multivitamin and folic acid supplementation before the pregnancy could reduce the overall occurrence of congenital abnormalities and neural-tube defects<sup>[26]</sup>. Moreover, the public health system bears the consequences of political and economic decisions made elsewhere in society, and this is especially prominent in cities with large populations like Shanghai<sup>[27]</sup>. The current study reported that permanent residents have a lower risk of birth defects, but this finding requires further investigation of the influence of genetic, cultural and environmental factors on birth defects. In the entire migrant population, the proportion of women aged < 20, ≥ 20 but < 25, ≥ 25 but < 35 and ≥ 35 was 1.0%, 14.9%, 9.5%, and 2.0%, respectively, which was higher than the corresponding proportion of all permanent residents in these age groups (0.2%, 7.7%, 6.9%, 1.0%, respectively).

The main findings of this study are consistent with those of previous studies, but other important results were also obtained, as described below. In our analysis, the prevalence of birth defects in caesarean deliveries was higher than that in vaginal deliveries during the same period. This might be due to larger fetuses, abnormal umbilical cords, and amnion or intrauterine infections, which negatively affect the health of the fetuses. The incidence of birth defects in twins and other types of multiple births was higher than that in singleton births.

In summary, birth defects are generally caused by several interrelated factors. Risk factors that contribute to birth defects include genetics, exposure to chemicals, physical and biological issues and maternal elements.

More than half of all birth defects cannot be attributed to a single factor<sup>[28]</sup>. It is thus a good idea to apply more complete prenatal examinations as well as to pay more attention to maternal health care and prenatal nutrition. To better understand the serial occurrence of birth defects in China, more hospitals should participate in this health network and launch nationwide multi-center studies. It is necessary to implement unified criteria and regular professional training for the diagnosis of birth defects, as well as to review the current knowledge of birth defects and promote more advanced technologies.

However, several limitations prohibited further analysis. First, this study was conducted by two departments at our hospital, and the results may not be generalizable to the Shanghai area. Second, the prevalence was not applicable to births < 28 wk of gestation. However, the numbers of births before 28 wk of gestation are much smaller compared with the number of births after 28 wk of gestation. Therefore, the impact of these births on the prenatal and perinatal prevalence of birth defects is expected to be minimal. This should, however, be further investigated in a future study. The individuals who manage the medical records of our hospital were contacted about the rate of induced termination of pregnancies due to prenatally diagnosed fetal anomalies, but these data were unavailable; this information would definitely alter the prevalence of defects diagnosed postnatally.

The current study used a large database to analyze neonatal congenital malformations and related risk factors. We found that higher gravidity, premature birth, lower birth weight, cesarean delivery, twin or multiple births and registration as part of a migrant population are high-risk factors for birth defects. Based on this result, the recommended interventions are as follows: (1) regular screening tests among pregnant women are needed at local health care sectors in Shanghai; and (2) despite the difficulty, the primary emphasis should be to enhance the management (provide more knowledge and training for pregnant women during the prenatal period) and health care (such as folic acid supplementation) of women in migrant populations in the future.

## ARTICLE HIGHLIGHTS

### Research background

In the 1980s, China implemented a birth defect surveillance system. Approximately 470 hospitals in 31 provinces, municipalities and autonomous regions in the nation participate in this monitoring network; this three-level monitoring network covers nearly 80 million people.

### Research motivation

Based on continuous dynamic monitoring, the authors obtained accurate and reliable data that were vital to the health of Chinese women and their children, and provided a scientific basis for decision-making regarding maternal and neonatal health in the author's country.

### Research objectives

The objective of this study is to estimate the temporal trend and epidemiologic

characteristics of birth defects at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai from 2008 to 2014.

### Research methods

This report describes a population-based study of all births at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China from January 2008 to December 2014. A logistic regression analysis was used to identify the parameters that are independently associated with birth defects.

### Research results

A total of 82814 births, including 824 cases of birth defects, were recorded. The rate of birth defects was 0.995 per 100 births. In the multivariable regression analysis, neonatal birth defects were likely to be associated with higher gravidity (OR = 1.099, 95%CI: 1.024-1.178), premature birth (OR = 1.905, 95%CI: 1.501-2.418), low birth weight (OR = 3.844, 95%CI: 3.004-4.919), twin births or higher order multiple pregnancies (OR = 1.477, 95%CI: 1.107-1.969), cesarean delivery (OR = 1.184, 95%CI: 1.016-1.380) and registration as part of a migrant population (OR = 1.380, 95%CI: 1.167-1.632). Female infants were less likely to have birth defects than male infants (OR = 0.710, 95%CI: 0.616-0.818).

### Research conclusions

Higher gravidity, premature birth, lower birth weight, twin births or higher order multiple pregnancies, and registration as part of a migrant population are independent predictors of birth defects.

### Research perspectives

Based on this result, the recommended interventions are as follows: (1) regular screening tests among pregnant women are needed at local health care sectors in Shanghai; and (2) despite the difficulty, the primary emphasis should be to enhance the management (provide more knowledge and training for pregnant women during the prenatal period) and health care (such as folic acid supplementation) of women in migrant populations in the future.

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## Case Control Study

## Is nitric oxide level affected in postmenopausal women with hypothyroidism?

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**Author contributions:** Dahiya K and Dalal D contributed equally to the work; Dahiya K, Dalal D, Malhotra V and Aggarwal S designed the research work; Malhotra V and Aggarwal S treated the patients; Dahiya K and Dalal D collected material and clinical data from patients; Dahiya K, Dalal D and Ghalaut VS performed the assays; Dalal D, Malik AK and Dahiya P analyzed data; Dahiya K, Dahiya P and Dalal D wrote the paper. Malhotra V, Aggarwal S, Malik AK and Ghalaut VS approved the final version of the manuscript.

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### Abstract

#### AIM

To analyze serum levels of nitric oxide (NO), an indicator of cardiovascular health, in post-menopausal females with and without hypothyroidism.

#### METHODS

NO was analyzed colorimetrically in 30 newly diagnosed hypothyroid postmenopausal females and 30 postmenopausal females with normal thyroid profile. Results were compared and subjected to appropriate statistical

analysis.

## RESULTS

The levels of serum NO were found to be significantly decreased in postmenopausal females with hypothyroidism as compared to the levels in those with normal thyroid profile ( $P$  value < 0.05). A negative correlation of NO was observed with thyroid stimulating hormone whereas a positive correlation of NO was observed with free T3 (FT3), free T4 (FT4), T3 and T4 though it was statistically significant only for FT4 among postmenopausal females with hypothyroidism.

## CONCLUSION

Postmenopausal hypothyroid females may be at a risk of compromised cardiovascular health as indicated by low NO levels. Regular monitoring and risk assessment is essential for timely intervention.

**Key words:** Nitric oxide; Menopause; Thyroid profile; Hypothyroidism; Cardiovascular health

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**Core tip:** It is already established that post-menopausal women on account of low levels of reproductive hormones are at a greater risk of cardiovascular accidents. Hypothyroidism, itself, is also a risk factor for poor cardiovascular health. In this study, significantly low levels of nitric oxide (NO) were observed in postmenopausal hypothyroid females as compared to those in postmenopausal euthyroid females, thereby, indicating the significant role played by NO in cardioprotection as well as a need for regular monitoring of NO levels and thyroid profile in postmenopausal phase of life.

Dahiya K, Dalal D, Malhotra V, Aggarwal S, Malik AK, Ghalaut VS, Dahiya P. Is nitric oxide level affected in postmenopausal women with hypothyroidism? *World J Obstet Gynecol* 2017; 6(3): 16-20 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v6/i3/16.htm> DOI: <http://dx.doi.org/10.5317/wjog.v6.i3.16>

## INTRODUCTION

Menopause is a physiological process characterized by loss of reproductive function, depletion of ovarian follicles and estrogen production resulting in appearance of a variety of symptoms including irregular menstruation, vasomotor instability (hot flashes and night sweats), genitourinary tissue atrophy, breast tenderness, vaginal dryness, mood variations and increased propensity for developing osteoporosis and heart disease<sup>[1,2]</sup>.

Estrogen is found to be protective against cardiovascular disease by a variety of mechanisms including favorable effects on lipoprotein, glucose and insulin homeostasis, changes in extracellular matrix composition, atherosclerotic plaque destabilization and the facilitation

of collateral vessel formation<sup>[2]</sup>. Postmenopausal estrogen deficiency is associated with higher blood levels of free fatty acids which contribute to the pathogenesis of the metabolic syndrome and insulin resistance, symptoms of which might, sometimes, overlap with those of hypothyroidism<sup>[3]</sup>.

Hypothyroidism is a condition resulting from inadequate production of thyroid hormones and is characterized by increased levels of thyroid stimulating hormone (TSH) and low levels of T<sub>3</sub> and T<sub>4</sub>. Hypothyroidism is of two types, primary and secondary, depending on the organ of defect<sup>[4]</sup>. The prevalence of primary hypothyroidism is 10/1000 in general population<sup>[3]</sup>. It is more common in women than men. The ratio of female to male is approximately 6:1<sup>[5]</sup>. Studies have shown a relationship between thyroid hormones and nitric oxide (NO). According to a report, thyroid hormone can induce endothelium independent relaxation<sup>[6,7]</sup>. One of these studies showed that expression of both endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) was modulated in thyroid disorders<sup>[7]</sup>.

NO is recognized as a cellular signaling molecule which plays many important roles in the body. Important biological functions of NO include maintenance of blood pressure, facilitating neuro-transmission, regulating platelet functions and modulation of the immune system<sup>[8]</sup>. It is synthesized from amino acid L-Arginine which gets oxidized to NO by the action of the NOS enzymes<sup>[9]</sup>. Pathophysiological basis of cardiovascular changes is reported to be endothelial dysfunction which occurs mainly *via* a decrease in endothelium-dependent vasodilatation mediated by NO<sup>[10]</sup>.

Some studies have suggested that estrogen associated cardio-protection is mediated by estrogen induced increase in the release of NO from the vascular endothelium<sup>[11,12]</sup>. This finding was recently confirmed in post-menopausal women, in whom estradiol was observed to be acutely attenuated and they showed abnormal coronary vasomotor responses to acetylcholine<sup>[11]</sup>. With all this background information in mind, this study was planned to estimate NO levels in postmenopausal hypothyroid and euthyroid females.

## MATERIALS AND METHODS

### Study design and setting

Thirty postmenopausal women with newly diagnosed primary hypothyroidism (group A, diagnosed by increased TSH and clinical examination) and thirty euthyroid controls (group B) presenting as outdoor patients in Department of Obstetrics and Gynecology/Department of Endocrinology were included in the study. All the subjects were enrolled after obtaining their informed consent and taking care of all ethical issues including approval from Postgraduate Board of Studies of the Institute. The sample size was calculated keeping power of the test at 9.0<sup>[13]</sup>.

### Exclusion criteria

Subjects with any other chronic disease or on any type

**Table 1** Comparison of various parameters among postmenopausal hypothyroid (group A) and postmenopausal euthyroid (group B) females

Parameters	Group A	Group B	P value
Body mass index (kg/m <sup>2</sup> )	30.37 ± 3.26	29.03 ± 3.56	0.993
TSH (μIU/mL)	9.596 ± 2.349 (5.9-15.5)	3.663 ± 1.193 (0.94-4.4)	< 0.001
S. T4 (ng/mL)	1.262 ± 0.707 (0.93-2.1)	6.405 ± 1.727 (3.2-9.2)	< 0.001
S. T3 (ng/mL)	56.266 ± 15.72 (22-77)	98.433 ± 9.640 (85-111)	< 0.001
FT3 (pg/dL)	0.493 ± 0.180 (0.09-0.83)	1.230 ± 0.213 (2.1-4.1)	< 0.001
FT4 (ng/mL)	1.206 ± 0.352 (0.93-2.1)	2.835 ± 0.507 (0.93-1.8))	< 0.001
NO (μmol/L)	25.832 ± 5.286 (16.5-38)	33.671 ± 5.173 (23.16-47)	< 0.001

NO: Nitric oxide; TSH: Thyroid stimulating hormone.

of treatment were excluded from the study.

### Sample collection, analyses and recruitment of cases

Venous blood samples were collected aseptically from all recruited subjects and serum was separated. Serum samples of all the subjects were analyzed for complete thyroid profile including total T<sub>3</sub> (TT<sub>3</sub>), total T<sub>4</sub> (TT<sub>4</sub>), free T<sub>3</sub> (FT<sub>3</sub>), free T<sub>4</sub> (FT<sub>4</sub>), TSH and NO on the same day of collection. TT<sub>3</sub>, TT<sub>4</sub> were estimated by standard radioimmunoassay, TSH by immunoradiometric assay and FT<sub>3</sub> and FT<sub>4</sub> were analyzed using a chemiluminescence technique (Advia Centaur CP, Siemens). Newly diagnosed primary subclinical and overt hypothyroidism (TSH > 4.25 μIU/mL, free T<sub>3</sub> < 2.4 pg/mL, free T<sub>4</sub> < 0.7 ng/dL) in postmenopausal women (> 1 year of menopause but < 2 years of menopause) assessed on the basis of history, clinical examination and thyroid function tests were included in the study group A and postmenopausal women (> 1 year of menopause but < 2 years of menopause) assessed on the basis of history, clinical examination and normal thyroid function test were included in the study group B.

NO was measured colorimetrically using Griess reaction which measures nitrite formed from NO which is a stable and nonvolatile end product of NO which, itself, has a short half-life of 6-10 s. In this method, nitrite reacts under acidic conditions with sulfanilic acid to form a diazonium cation which subsequently couples to the aromatic amine 1-naphthylamine to produce a purple coloured complex whose absorbance is read at 546 nm<sup>[14]</sup> body mass index (BMI) was also calculated and recorded for these patients.

### Statistical analysis

Data of both the groups was compared using student's *t*-test while the correlation was calculated using Pearson's coefficient of correlation.

## RESULTS

The mean age of postmenopausal females in group A was 53.2 ± 1.57 years with a range of 51-57 years and in group B 52.8 ± 2.38 years with range being 46-57 years (*P* = 0.492). Hypothyroid patients were found to have greater BMI as compared to euthyroid subjects

but it was statistically non-significant (*P* = 0.993). The levels of thyroid profile and NO in both the groups are shown in Table 1. Serum NO levels were observed to be significantly decreased in patients (group A) as compared to those in controls (group B) (*P* value < 0.05).

In group A, a negative correlation of NO was observed with TSH whereas a positive correlation of NO was found with FT<sub>3</sub>, FT<sub>4</sub>, T<sub>3</sub> and T<sub>4</sub> (Table 2). Amongst all, only FT<sub>4</sub> was found to have a statistically significant correlation with NO (*P* value = 0.04) (Figure 1). In group B, a positive correlation of NO was observed with T<sub>3</sub>, T<sub>4</sub>, FT<sub>3</sub> and FT<sub>4</sub> though it was not significant statistically (Table 3).

## DISCUSSION

The natural menopause is defined as 12 consecutive months of amenorrhea according to some major studies<sup>[15-17]</sup>. The present study included recently menopausal women with duration of menopause of more than one year but less than 2 years, to minimize the age related effects. There could be age-related fall in circulating T<sub>4</sub> concentrations which could result in increased TSH secretion. Alternatively, with aging there is reduction in TSH bioactivity, the responsiveness of the thyroid to TSH or some occult thyroid disease, leading to increased TSH levels<sup>[18]</sup>. With aging, there is progressive decline of glutathione concentration in cells of liver, kidney and retina etc. Thus, the functioning of various organs is affected due to increased reactive oxygen species, mitochondrial damage and cellular dysfunction. The first year of menopause is considered as menopause transition phase, during which there are ongoing changes in hormonal levels. Studies have demonstrated that, the potential for hormone secretion by residual follicles in older women is variably diminished<sup>[19,20]</sup>.

In this study, BMI of postmenopausal hypothyroid females was observed to be 30.37 ± 3.26 kg/m<sup>2</sup>, which was slightly higher than the BMI of postmenopausal euthyroid females, which was 29.03 ± 3.56 kg/m<sup>2</sup>. This increase in BMI in postmenopausal hypothyroid females is due to various factors because of decreased estrogen and thyroid hormone levels in these females. Some

**Table 2** Correlation of nitric oxide with different parameters in group A

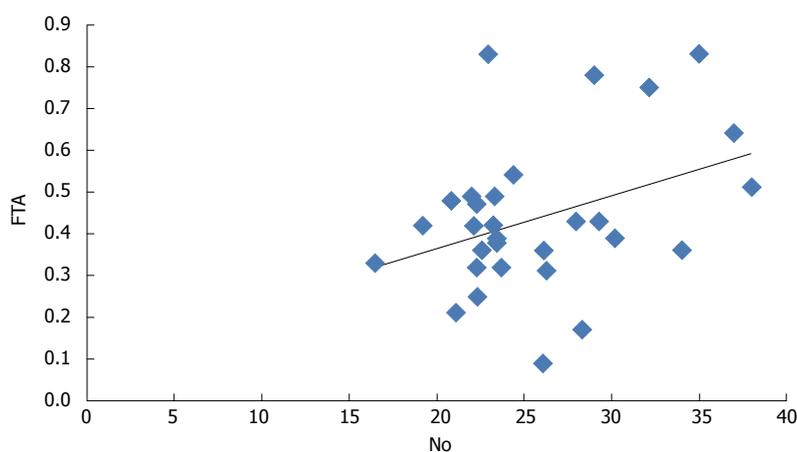
Parameter	r value	P value
Estrogen	0.21	0.24
Progesterone	-0.14	0.43
TSH	-0.1	0.58
T4	0.36	0.50
T3	0.16	0.38
Free T3	0.22	0.22
Free T4	0.37	0.04

TSH: Thyroid stimulating hormone.

**Table 3** Correlation of nitric oxide with different parameters in group B

Parameter	r value	P value
Estrogen	0.13	0.47
Progesterone	-0.06	0.72
TSH	0.00	0.97
T4	0.17	0.36
T3	0.17	0.35
Free T3	0.26	0.15
Free T4	0.31	0.09

TSH: Thyroid stimulating hormone.

**Figure 1** Scatter diagram showing correlation of nitric oxide (X-axis) with free T4 (Y-axis) in Group A ( $r = 0.37$ ,  $P = 0.04$ ). NO: Nitric oxide.

studies have also proposed that postmenopausal women have higher BMI than premenopausal women because of action of estrogen<sup>[21,22]</sup>.

In the present study, NO levels in postmenopausal hypothyroid females were observed to be significantly lower than those in postmenopausal euthyroid females ( $P = 0.00$ ). In a study, NO levels were observed to be higher ( $75 \pm 5 \mu\text{mol/L}$ ) in postmenopausal healthy females<sup>[23]</sup>. In another study, NO levels were increased significantly in hypothyroid females ( $57.61 \pm 15.8 \mu\text{mol/L}$  and  $36.24 \pm 7.61 \mu\text{mol/L}$  in postmenopausal hypothyroid and euthyroid females respectively). Above study observed a positive correlation between TSH and NO.

In the present study, a negative correlation was observed between TSH and NO but it was not statistically significant ( $P = 0.58$ ). The correlation of NO with free T<sub>4</sub> was found to be statistically significant in postmenopausal hypothyroid females with a "r" value of 0.37 and P value of 0.04. Thyroid hormones directly increase NO production in vascular smooth muscle cells through PI3K/Akt signaling pathway and produce rapid relaxation of vascular smooth muscle cells. T<sub>3</sub> is reported to significantly induce the expression of three NOS isoforms in smooth muscle cells<sup>[23]</sup>.

Various studies have shown relationship between thyroid hormone and NO and that thyroid hormone can also induce endothelium-independent relaxation<sup>[24,25]</sup>

but data from some studies suggest that smooth muscle cells rather than the endothelium, are the primary target of thyroid hormones<sup>[19]</sup>. One study in rats showed that the hyperthyroid state was associated with increased formation of NO, but there was a reduced capacity for responding to NO when compared to the hypothyroid state<sup>[26]</sup>. The same study showed that both eNOS and nNOS expression were modulated in hypothyroidism and hyperthyroidism. Another study on rats showed that thyroid hormones affect the level and activity of nNOS and therefore NO levels.

Thus, it may be concluded that cardiovascular health is compromised in postmenopausal women which is further deteriorated by hypothyroidism, indicated by lower NO levels in postmenopausal hypothyroid women as compared to postmenopausal euthyroid women. This indicates that normal level of thyroid hormone along with reproductive hormones is essential for cardiac health. Further, regular monitoring and risk assessment regarding cardiovascular disease is essential in postmenopausal hypothyroid females and timely interventions may help to avoid further complications.

## ARTICLE HIGHLIGHTS

### Research background

Hypothyroidism and menopause, both pose a risk to the cardiac health of women.

### Research objectives

As suggested by literature that estrogen induced cardio protection might be mediated by release of nitric oxide (NO), this study was conducted to estimate and compare serum NO levels in postmenopausal women with and without hypothyroidism.

### Research methods

NO was analyzed as nitrite colorimetrically in 30 postmenopausal hypothyroid and euthyroid females each.

### Research results

A statistically significant decrease was observed in NO levels in postmenopausal hypothyroid females as compared to their euthyroid counterparts ( $P < 0.05$ ).

### Research conclusions

It may be concluded that cardiovascular health is compromised in postmenopausal women because of low estrogen, which is further deteriorated by hypothyroidism, indicated by lower NO.

### Research perspectives

This research directs towards future perspectives in analyzing other endothelial function markers along with actual estimation of NO and its association with reproductive hormone levels in larger study groups.

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