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ORIGINAL ARTICLE

Risk factors for congenital anomalies in high risk pregnant women: A large study from South India

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High Risk Pregnancy;
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Abstract *Background:* High Risk Pregnancy (HRP) is a condition where mother or developing fetus or both are at increased risk of complications during or after pregnancy and birth. There are no studies so far which have characterized congenital anomalies (CAs) in HRP women with different previous obstetric histories.

Aim: The present study was aimed to determine the prevalence, types and distribution of various CAs and also to find out the exact risk factors for different obstetric histories.

Subjects and methods: A total of 3301 HRP women (2011–2014) were enrolled. Diagnosis was made using 3D/4D ultrasound. Serum was analyzed for IgG & IgM against TORCH (Toxoplasma, Rubella, CMV and HSV) agents by ELISA. Eleven percent were pregnant women carrying fetuses with CAs in the present pregnancy, while remaining 89% were with bad obstetric history (BOH) and other medical and obstetric complications.

Results: Eleven percent pregnant women were carrying fetuses with CAs in the present pregnancy. The major CAs observed were Central Nervous System (CNS) followed by renal anomalies. Maternal age ($\leqslant$25 years, OR = 1.42, $p = 0.002$), paternal age (<30 years, OR = 1.51, $p < 0.001$), consanguinity (OR = 1.39, $p = 0.012$) and primi gravida (OR = 3.40, $p < 0.001$) were identified as risk factors for HRP women with fetal CAs in present pregnancy. Maternal age $\leqslant$25 years and paternal age <30 years conferred around 2-fold risk toward CAs in primi gravida women ($p < 0.001$) whereas consanguinity was associated with CAs in HRP women with BOH (OR = 1.95, $p < 0.018$). Toxoplasmosis played a significant role in pregnant women with CAs in present pregnancy with previous normal pregnancies (OR = 4.45, $p = 0.009$).

Conclusion: High prevalence of CAs was found in HRP women compared to general population. Low parental age contributed toward CAs in primi gravida women while consanguinity was found to be a predisposing factor for CAs in HRP with previous BOH. Toxoplasmosis conferred risk for CAs in HRP women with previous normal pregnancies.

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1. Introduction

High Risk Pregnancy (HRP) is a condition where the mother or the developing fetus or both are at an increased risk for complications during or after pregnancy and birth [1]. Congenital anomalies are the leading causes of mortality in developed and developing countries [2]. Approximately 50% of all congenital malformations cannot be linked to a specific cause. BOH implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, history of intrauterine fetal death, intrauterine growth retardation, stillbirth, early neonatal death and congenital anomalies.

Till date several studies in developed countries have been performed to assess the determinants for HRP but the risk factors varied with respect to different ethnic groups [3–4]. In addition, there are no studies so far which have characterized congenital anomalies in HRP women with different previous obstetric histories. Thus, the present study was aimed to determine the prevalence, types and distribution of various CAs and also to find out the exact risk factors for different obstetric histories.

2. Subjects and methods

A total of 3301 HRP women attending antenatal clinic of Modern Government Maternity Hospital, Hyderabad during 3 years (2011–2014) were enrolled. Diagnosis was made using 3D/4D ultrasound by fetal medicine specialists at Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Hyderabad. The anomalies identified were classified according to the International Classification of Disease, Tenth Revision codes (http://apps.who.int/classifications/). The HRP women were personally interviewed, counseled and the detailed history has been recorded in a special proforma with regard to demographic characteristics such as parental age, consanguinity, BOH, gravida, religion, parental education, occupation, socioeconomic status, and maternal infections like TORCH (Toxoplasma, Rubella, Cyto MegaloVirus and Herpes Simplex Virus) etc. Pregnant women with congenital anomalies in present pregnancy, BOH, maternal diabetes, hypertension, epilepsy etc., were included in the study. The work has been carried out in accordance with the code of Ethics of The World Medical Association for experiments in humans. Study was approved by the Institutional Ethics Committee and informed consent was obtained from all pregnant women prior enrollment.

Two milliliter of blood was aseptically drawn by venipuncture into a tube containing clot activator from a total of 291 HRP women with fetal CAs in the present pregnancy. They were then centrifuged and serum was separated. The levels of IgG and IgM were measured using commercially available ELISA kits (Euroimmun, Germany), and Optical Density (OD) was measured at 450 nm in a microplate ELISA reader (Bio-Rad, USA) according to manufacturer instructions. The results were interpreted on the basis of Immune Status Ratio (ISR) index calculated by dividing the specimen OD value by the cut-off calibrator ratio. The tests were considered seropositive if ISR value is $\geqslant 1.11$ and considered seronegative if ISR $\leqslant 0.9$. Samples with an ISR value in between 0.9 and 1.10 were considered equivocal.

Statistical analysis was performed using test of proportion online calculator (http://in silico.net/tools/statistics/ztest/) and openepi software (http://www.openepi.com). Differences between groups were determined by $\chi 2$ test and risk analysis was performed by calculating Odds ratio (OR) at 95% CI. A two tailed p-value of < 0.05 was considered to be significant.

3. Results

Out of 3301 HRP women, 11% (360/3301) were pregnant women carrying fetuses with CAs in the present pregnancy (Group 1), while remaining 89% (2941/3301) were with BOH and other medical and obstetric complications (Group 2). Out of 360 pregnant women, 130 (36%) were primi gravida pregnant women with fetal CAs in the present pregnancy, 145 (40%) were pregnant women with fetal CAs in present pregnancy with previous normal pregnancies while remaining 85(24%) were pregnant women with fetal CAs in present pregnancy with previous BOH. Among 89% of HRP women with BOH and other medical and obstetric complications, 72% (2379) were with BOH, 12% (401) of women presented with hypertension, heart disease, diabetes, epilepsy etc., while 161 (5%) HRP women were carrying twins or triplets (Fig. 1).

When the identified congenital anomalies were classified according to the International Classification of Disease, the most common system affected was central nervous system (CNS) (37%) [isolated hydrocephalous, hydrocephalous with neural tube defect, microcephaly, choroid plexus cyst, intra cardiac focus, dilatation of occipital horn of right lateral ventricle, holoprosencephaly, cystic hygroma with gross hydrocephalous, bilateral ventriculomegaly, dandy walker malformations, Arnold Chiari malformation, giant cisterna magna, anencephaly, meningomyelocele, encephalocele, spina bifida etc.], followed by renal anomalies (20%) [dysplastic kidneys, poly cystic kidneys, multi cystic kidneys, hydronephrosis, echogenic kidneys, bilateral pyelectiasis, bilateral renal pelvis prominent, horse shoe kidney, membrano proliferative glomerular nephritis, asymmetric dilatation etc.], multiple anomalies (11%) [congenital heart disease with omphalocele and cleft lip, bilateral club foot with hydrocephalous, hydronephrosis with hydrocephaly, gross hydrocephalus with cleft lip and cleft palate, IUGR with fetal left hydronephrosis, hydrocephalus with dysplastic kidneys, kyphoscoliosis with omphalocele, club foot and club hands with hydrocephalus, dandy walker with congenital left diaphramatic hernia, hydrocephalus with renal dysplasia, anencephaly with omphalocele, hydrocephalus with dysplastic kidneys, dilated ventricles with multiple anomalies of the abdomen-ascites, pleural effusion, hydrops fetalis, cystic hygroma with skeletal deformity, single umbilical artery with hyper echogenic bowels and lungs, echogenic bowels with left kidney pyelectasis, asymmetry of fetal heart chambers with bilateral hydronephrosis, fetal congenital diaphramatic hernia with occipital encephalocele, kyphoscoliosis with spina bifida, sacral meningocele and omphalocele, fetal spina bifida with club foot, kyphoscoliosis with lateral ventricle prominent, anencephaly with diaphramatic hernia and left hydro utero nephrosis, club foot with omphalocele and spinal deformity etc.], musculoskeletal system [kyphoscoliosis, achondroplasia, recurrent osteogenesis imperfecta, dwarfism, brachycephaly, hemi vertebrae, dolicocephalus,

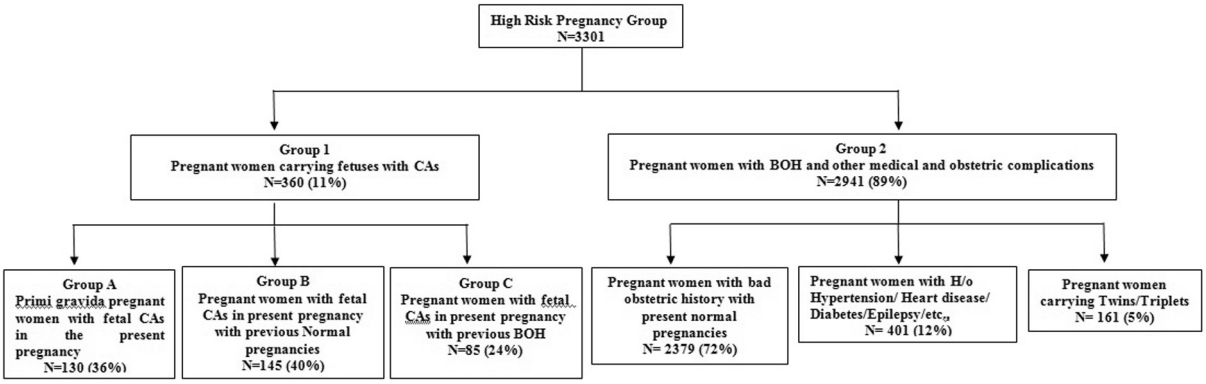

Figure 1 Characteristics of High Risk Pregnancy (HRP) Group.

bilateral talipes equinogenesis, short limbs, club foot, fetal lower limb deformity] were seen in 8% cases, Gastrointestinal tract abnormalities [omphalocele, gastroschisis, duodenal atresia, absent stomach bubble, esophageal atresia, echogenic bowel, anterior abdominal wall defect, absent fetal gastric bubble, exomphalocele etc.] were found in 6% cases. Cardiovascular System disorders [atrial and ventricular septal defects, pericardial effusion, small sized pulmonary artery, over riding of aorta, cardiomegaly, single atrium, small foci in left ventricle, left heart hypoplasia etc.] were detected in 5% cases. Lymphatic defects [cystic hygroma, hydrops fetalis, ascites, absent nasal bone] were found in 4% cases. Respiratory system disorders [bilateral pleural effusion, diffusely hyperechoic, narrowing of chest wall] were seen in 1% of the cases. Urinary system defects [hydroureters, pelvi ureteric junction (PUJ) obstruction, megacystis] were observed in 1% of the cases. Syndromes [Meckel-Gruber syndrome, Holt Oram syndrome, Turners syndrome - fetal hydrops and cystic hygroma] were observed in 1% of the cases. Facial anomalies [cleft lip, cleft palate, cleft lip of fortus, cleft lip and palate] were detected in 1% of the cases (Fig. 2).

Demographic characteristics among these groups revealed maternal age $\leqslant$25 years [OR = 1.42(1.31–1.78), $p = 0.002$], paternal age $<$30 years [OR = 1.51(1.20–1.90), $p < 0.001$] and consanguinity [OR = 1.39(1.08–1.80), $p = 0.012$] as the predisposing factors toward CAs for Group 1. Additionally, primi gravida women of Group 1 were also more likely (3-fold) to have fetal anomalies [OR = 3.40(2.68–4.31), $p < 0.001$] (Table 1).

Group 1 women were carrying fetuses with CAs in the present pregnancy irrespective of their previous history of BOH or normal pregnancy or primi gravida. Thus, they were further classified into three sub-groups viz. Group A – Primi gravida pregnant women with fetal CAs in present pregnancy, Group B – Pregnant women with fetal CAs in present pregnancy with previous normal pregnancies and Group C – Pregnant women with fetal CAs in present pregnancy with previous BOH. Detailed evaluation of the groups with respect to epidemiological factors and TORCH infections, demonstrated a significant contribution of $\leqslant$25 years maternal age [OR = 2.35(1.46–3.79, $p < 0.001$], and $<$30 years paternal age [OR = 2.30(1.41–3.74), $p < 0.001$], toward group A whereas consanguinity [OR = 1.95(1.15–3.31), $p = 0.018$] was associated with group C (Table 2). Evaluation of seropositivity for TORCH agents within the sub-groups (A, B and C), did not show its influence toward CAs in groups A and C. However, HRP women in group C showed 4.45 fold risk for having fetal CAs in present pregnancy [OR = 4.45(1.44–12.5), $p = 0.009$] (Table 3).

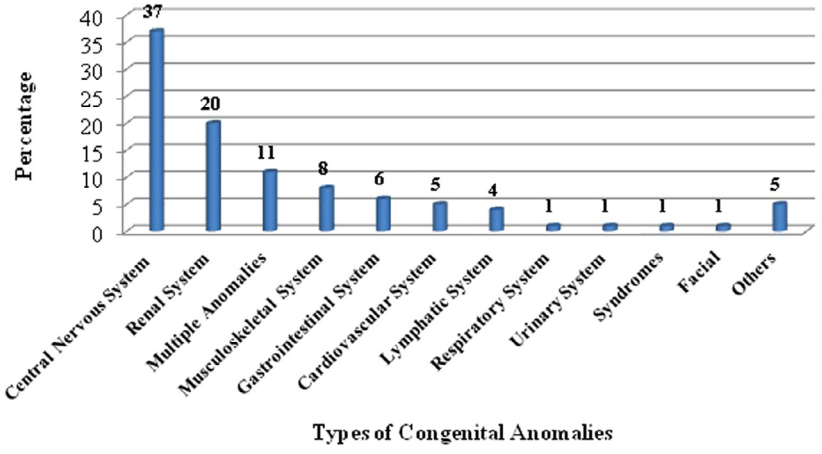

Figure 2 Distribution of congenital anomalies in group 1.

Table 1 Distribution of demographic characteristics in Group 1 and Group 2.

Variable	Group 1 N(%) 360	Group 2 N(%) 2941	OR(95%CI)	*p*-value
Maternal age				
⩽25 yrs	228(63)	1613(55)	1.42(1.13–1.78)	S
>25 yrs	132(37)	1328(45)		
Paternal age				
<30 yrs	236(65)	1638(56)	1.51(1.20–1.90)	S
⩾30 yrs	124(35)	1303(44)		
Consanguinity				
Yes	90(25)	567(19)	1.39(1.08–1.80)	S
No	270(75)	2374(81)		
Gravida				
Primi gravida	130(38)	419(14)	3.40(2.68–4.31)	S
Multi gravida	230(62)	2522(86)		
Religion				
Hindu	248(69)	1925(66)	1.16(0.92–1.47)	NS
Muslim	112(31)	1016(34)		
Maternal Education				
Primary and less	126(35)	1059(36)	0.95(0.76–1.2)	NS
Secondary and above	234(65)	1882(64)		
Paternal education				
Primary and less	187(52)	1529(52)	0.99(0.80–1.24)	NS
Secondary and above	173(48)	1412(48)		
Maternal occupation				
House wives	314(88)	2649(90)	0.75(0.53–1.04)	NS
Laborers	19(5)	141(5)	1.10(0.67–1.81)	NS
Agricultural workers	15(4)	71(2)	1.75(0.99–3.10)	NS
Professionals	12(3)	80(3)	1.23(0.66- 2.28)	NS
Paternal occupation				
Drivers	77(21)	588(20)	1.08(0.83–1.42)	NS
Agricultural workers	67(19)	537(18)	1.02(0.77–1.35)	NS
Professionals	67(19)	531(18)	1.03(0.78–1.37)	NS
Laborers	51(14)	542(18)	0.73(0.53–0.99)	NS
Traders	48(13)	371(13)	1.06(0.77–1.47)	NS
Technical workers	29(8)	239(8)	0.99(0.66–1.48)	NS
Industrial	16(5)	107(4)	1.23(0.72–2.10)	NS
Hospital workers	5(1)	26(1)	1.57(0.47–4.21)	NS
Family Income				
<10,000	336(93)	2775(94)	0.83(0.53–1.30)	NS
>10,000	24(7)	166(6)		
Maternal diabetes/hypertension/ /epilepsy/heart disease etc.				
Yes	40(11)	401(12)		NS
No	320(89)	2540(88)	0.79(0.56–1.11)	
Family H/o congenital anomalies/mental retardation/genetic diseases				
Yes	36(10)	353(12)		
No	324(90)	2588(86)	0.81(0.56–1.17)	NS

Group 1 – High risk pregnant women carrying fetuses with CAs in the present pregnancy.
Group 2 – High risk pregnant women with History of repeated abortions, previous CAs, previous intra uterine deaths, previous neonatal deaths, previous preterm births and other medical & obstetric complications.
OR: Odds ratio, CI: Confidence Interval.
$p < 0.05$ is considered to be statistically significant, S – Significant, NS – Non-significant.

4. Discussion

High Risk Pregnancy is a major worldwide health problem demonstrating an increased risk of perinatal and maternal mortality. The present study was attempted to evaluate the burden of CAs in HRP women and also to assess the risk factors contributing to HRP as CAs are among the major causes of morbidity and mortality in many countries around the world. To the best of our knowledge the present study is the first of this kind in India.

In our study, 11% of CAs observed was almost double than reported among the general population in India (6%) [5]. The joint World Health Organization (WHO) and March of Dimes (MOD) meeting reported that 7% of all neonatal mortality

Table 2 Distribution of demographic characteristics in groups A, B and C of Group 1.

Variable	Group A (n = 130)	Group B (n = 145)	Group C (n = 85)	A vs. Others		B vs. Others		C vs. Others	
	n (%)	n (%)	n (%)	OR	p-value	OR	p-value	OR	p-value
Maternal age									
⩽25 yrs	98 (75)	84 (58)	46 (54)						
>25 yrs	32 (25)	61 (42)	39 (46)	2.35(1.46–3.79)	S	0.67(0.43–1.04)	NS	0.60(0.36–0.98)	NS
Paternal age									
<30 yrs	100 (77)	86 (59)	50 (59)						
⩾30 yrs	30 (23)	59 (41)	35 (41)	2.30(.1.41–3.74)	S	0.63(0.40–0.98)	NS	0.68(0.41–1.12)	NS
Consanguinity									
Yes	25 (19)	35 (24)	30 (35)						
No	105 (81)	110 (76)	55 (65)	0.60(0.35–1.01)	NS	0.92(0.56–1.50)	NS	1.95(1.15–3.31)	S
Gravida									
Primi gravida	130 (100)	0 (0)	0(0)	–	–	–	–	–	–
Multi gravida	0 (0)	145 (100)	85 (100)						
Religion									
Hindu	93 (72)	95 (66)	60 (71)						
Muslim	37 (28)	50 (34)	25 (29)	1.21(0.76–1.94)	NS	0.76(0.48–1.21)	NS	1.11(0.65–1.88)	NS
Maternal education									
Primary and less	43 (33)	46 (32)	37 (44)						
Secondary and above	87 (67)	99 (68)	48 (56)	0.87(0.55–1.37)	NS	0.78(0.50–1.22)	NS	1.61(0.97–2.65)	NS
Paternal education									
Primary and less	59 (45)	84 (58)	44 (52)						
Secondary and above	71 (55)	61 (42)	41 (48)	0.66(0.42–1.02)	NS	1.49(0.97–2.28)	NS	0.99(0.60–1.61)	NS
Maternal occupation									
House wives	112 (86)	128 (88)	74 (87)	0.86(0.45–1.62)	NS	1.17(0.61–2.22)	NS	0.98(0.47–2.02)	NS
Laborers	9 (7)	5 (4)	5 (6)	1.63(0.64–4.13)	NS	0.51(0.18–1.45)	NS	1.16(0.40–3.33)	NS
Agricultural	5 (4)	6 (4)	4 (5)	0.88(0.29–2.63)	NS	0.98(0.34–2.83)	NS	1.18(0.26–4.13)	NS
Professionals	4 (3)	6 (4)	2 (2)	0.88(0.19–3.36)	NS	1.50 (0.39–5.74)	NS	0.63(0.06–3.08)	NS
Paternal occupation									
Drivers	21 (16)	35 (24)	21 (25)	0.59(0.34–1.04)	NS	1.31(0.78–2.17)	NS	1.28(0.72–2.27)	NS
Agricultural	25 (19)	28 (19)	14 (16)	1.06(0.61–1.84)	NS	1.08(0.63–1.85)	NS	0.82(0.43–1.57)	NS
Professionals	28 (22)	23 (16)	16 (19)	1.34(0.78–2.31)	NS	0.73(0.42- 1.27)	NS	1.01(0.54–1.89)	NS
Laborers	16 (12)	17 (12)	18 (21)	0.78(0.41–1.47)	NS	0.70(0.37–1.32)	NS	1.97(1.04–3.71)	NS
Traders	21 (16)	21 (15)	6 (7)	1.44(0.78–2.68)	NS	1.17(0.63–2.17)	NS	0.42 (0.17–1.02)	NS
Technical workers	10 (8)	15 (10)	4 (5)	0.92(0.41–2.05)	NS	1.65(0.77–3.54)	NS	0.49(0.16–1.46)	NS
Industrial	7 (5)	4 (3)	5 (6)	1.39(0.50–3.84)	NS	0.47(0.15–1.51)	NS	1.49(0.39–4.84)	NS
Hospital workers	2 (2)	2 (1)	1 (1)	1.18(0.09–10.4)	NS	0.98(0.08–8.74)	NS	0.80(0.01–8.30)	NS
Family income									
<10,000	118 (91)	139 (96)	79 (93)						
>10,000	12 (9)	6 (4)	6 (7)	0.54(0.23–1.24)	NS	2.11(0.81–5.46)	NS	0.92(0.35–2.40)	NS

Group A – Primi gravida pregnant women with CAs in present pregnancy.
Group B – Pregnant women with CAs in present pregnancy with previous normal pregnancies.
Group C – Pregnant women with CAs in present pregnancy with previous BOH.
OR: Odds ratio, CI: Confidence Interval.
$p < 0.05$ is considered to be statistically significant, S – Significant, NS – Non-significant.

Table 3 TORCH infections in groups A, B and C of Group 1.

Type of pathogen	Group A (n = 81)				Group B (n = 145)				Group C (n = 65)			
	IgG + IgM N(%)	IgG N(%)	OR (95% CI)	p-value	IgG + IgM N(%)	IgGN(%)	OR (95% CI)	p-value	IgG + IgM N(%)	IgG N(%)	OR (95% CI)	p-value
T. gondii	3(4)	16(20)	2.86(0.47–12.0)	NS	7(5)	37(26)	4.45(1.44–12.5)	S	7(11)	13(20)	–	–
Rubella	6(7)	72(89)	1.68(0.48–5.34)	NS	5(3)	139(96)	0.53(0.19–1.48)	NS	0(0)	59(91)	–	–
CMV	3(4)	77(95)	0.60(0.10–2.26)	NS	9(6)	136(94)	1.30(0.54–3.12)	NS	0(0)	59(91)	–	–
HSV	4(5)	48(60)	1.39(0.31–4.86)	NS	1(1)	80(55)	0.18(0.00–1.19)	NS	0(0)	48(74)	–	–

Group A – Primi gravida pregnant women with CAs in present pregnancy.
Group B – Pregnant women with CAs in present pregnancy with previous normal pregnancies.
Group C – Pregnant women with CAs in present pregnancy with previous BOH.
OR: Odds ratio, CI: Confidence Interval, $p < 0.05$ is considered to be statistically significant, S – significant, NS – non-significant.
CMV-Cyto Megalo Virus; HSV-Herpes Simplex Virus.

and 3.3 million under five deaths were due to CAs [6]. The incidence of BOH among HRP women in the present study was 72%, which is significantly higher than a prospective study carried out in North Central India (5.27%) [7]. This wide disparity in the higher incidences of CAs and BOH in our study may be attributed to sample size variation and rapid improvements in prenatal diagnosis, inclusion of minor anomalies and geographical factors.

Surveillance of CAs in the present study demonstrated the highest frequency of CNS anomalies and is consistent with previous reports in various ethnic groups [8–10]. Studies by Sheeba et al. [11] and Akruti et al. [12] from India also reported CNS anomalies to be the most frequent anomalies in still borns and new borns [11–12]. However, there were no reports pertaining to CAs in HRP women. The second commonest anomaly observed was renal accounting for 20% of CAs and is almost ten times (0.2%) higher than that reported in a prospective study by Sanghvi et al. in Mumbai [13]. The variations in the frequencies could be due to genetic background, geographical area, socioeconomic and nutritional status. The 3D/4D ultrasound scanning performed prenatally for all HRP women has led to the improved detection of CAs in our study.

The fetuses with lethal CNS anomalies often die in-utero or in the immediate perinatal period. The other non-lethal CNS anomalies may present with functional abnormalities like neuro developmental failure ranging from mild mental retardation, seizures to severe neurological disability i.e., deafness, speech abnormalities and congenital ophthalmic abnormalities. Structural abnormalities associated with CNS anomalies include microcephaly, hydrocephalous etc. Renal abnormalities in fetus may frequently present with mild to severe pyelectasis and bladder dysjunction like in posterior urethral valves and other anatomical abnormalities like polycystic kidneys may be present as large hyper echogenic kidneys and multiple cystic lesions in multi cystic kidneys. Fetuses with the polycystic kidney are lethal. Multi cystic kidney and polycystic kidney may present with enlarged kidneys in postnatal life. Pyelectasis may present with the features ranging from recurrent urinary tract infections to renal failure. Cardiovascular abnormalities may present with simple anatomical abnormalities like defect in the septum to complete developmental failure of one of the ventricle and functional abnormalities and may present with abnormal rhythms. Postnatally, these cases may present with features ranging from cyanosis to failure to thrive. Often, the complete failure of development of ventricle and severe rhythm abnormalities are fatal. Gastrointestinal abnormalities vary from gastroschisis, omphalocele, imperforated anus, and intestinal obstruction at various levels. The frequently seen anatomical abnormality in respiratory system is congenital cystic adenomatoid malformation (CCAM). These are the common characteristics of the major systems.

Group 1 subjects with lower maternal age of $\leqslant$25 years and paternal age $<$30 years were at an increased risk of CAs during pregnancy and this was in accordance with previous reports [14–16]. The mechanism responsible for such association is not known [17]. However, this increased risk among younger parents could be due to interaction of unknown genetic factors or environmental factors. The identification of novel risk factors for CAs by thorough investigation of age-specific parental behaviors may provide insights into etio-pathophysiology and preventive strategies of CAs. Other factor that has been repeatedly found to be associated with CAs in South India is consanguineous marriage, where it is practiced as an important social culture. Nearly 20% of HRP women of our study were married either to first or second cousins. Among the subgroups, group 1 women revealed around 1.4 fold risk for CAs which corresponds to earlier studies [18–20]. The incidence of CAs is higher in offsprings born to consanguineous couples since they express the homozygous genes inherited from their common ancestors [21]. In addition, primi gravida was observed to be associated with increased prevalence of CAs which could be due to unknown causes and is consistent with the findings of Truong et al. [22].

HRP women of group 1 had fetal CAs in present pregnancy and presented with different obstetric histories. Hence to know the exact causative factors in each group, group 1 was divided into three groups (A, B and C). Distribution of demographic characteristics demonstrated that the factors like parental age conferred around 2 fold risk for CAs in primi gravida HRP women with CAs in the present pregnancy of group A, the mechanism for which is unknown. Consanguinity contributed toward HRP women with fetal CAs in the present pregnancy with BOH of group C.

Asymptomatic and chronic infections play a crucial role in pregnancy loss associated with CAs, BOH and HRP. Our previous report on TORCH infections in HRP women demonstrated that IgG rubella and IgG CMV have a predisposing role for HRP while IgG toxoplasmosis confers protection. In addition, toxoplasma and rubella were showing a predisposing role toward BOH and congenital malformations respectively [23]. Analysis of TORCH infections in the three subgroups,

demonstrated IgG and IgM seropositivity for toxoplasmosis in group B and revealed an OR of 4.45 indicating that these HRP women with present CAs and with previous normal pregnancies were having around 4 fold risk of having CA. These results indicate a recent infection of toxoplasma where the transmission rate is as high as 90% for third trimester [24].

Though the preconception folic acid administration is a routine practise in this country almost all the high risk pregnant women included in the study are illiterates and belong to rural areas. Such advice for preconception folic acid was not followed by these patients. We reiterated the fact that preconceptional folic acid supplementation plays a pivotal role in prevention of congenital anomalies and counseled them to seek medical advice well in advance before planning for next pregnancy and also advised them to consume foods which are rich in folic acid.

5. Conclusion

Our study is the first to determine the burden of CAs in HRP women. A high prevalence (11%) of CAs was found in these women compared to general population (6%). The major CAs observed were CNS followed by renal anomalies. Maternal age ($\leqslant$25 yrs), Paternal age (<30 yrs), primi gravida and consanguinity contributed to the burden of CAs in HRP. Additionally, $\leqslant$25 yrs maternal age and <30 yrs paternal age contributed toward CAs in primi gravida women. Consanguinity was found to be a predisposing factor for CAs in HRP with previous BOH while toxoplasma seropositivity conferred risk for pregnant women with CAs in present pregnancy with previous normal pregnancies. As CAs continue to be an important cause of morbidity and mortality especially in developing countries, advanced screening methods for early diagnosis of HRP may help in appropriate intervention and proper management of congenital anomalies.

Conflict of interest

No conflict of interest to declare.

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References

[1] Jonathan MC, Edward AJ, Eduardo C, Wellington PM, Luciano MMN, Antonio FM. Applicability of the rapid biophysical profile in antepartum fetal well-being assessment in high-risk pregnancies from a University Hospital in São Paulo, Brazil: preliminary results. ISRN Obstet Gynecol 2013. http://dx.doi.org/10.1155/2013/329542.

[2] Amar T, Krishna V, Pushpa C, Manish J. Congenital malformations at birth in Central India: a rural medical college hospital based data. Indian J Hum Genet 2010;16:159–63.

[3] Peter von D, Laura M. What matters in preeclampsia are the associated adverse outcomes: the view from Canada. Curr Opin Obstet Gynecol 2008;20:110–5.

[4] Hafez Samar K, Dorgham Laila Sh, Sayed Suheir AM. Profile of High Risk Pregnancy among Saudi Women in Taif-KSA. World. J Med Sci 2014;11:90–7.

[5] Tamoghna B. India launches programme for child-health screening. Lancet 2013;381.

[6] World health organization. Management of birth defects and haemoglobin disorders: report of a joint WHO-March of dimes meeting. Geneva, Switzerland, Geneva: WHO; 2006.

[7] Singh G, Sidhu K. Bad obstetric history: a prospective study. MJAFI 2010;66.

[8] Shawky RM, Sadik DI. Congenital malformations prevalent among Egyptian children and associated risk factors. Egypt J Med Hum Genet 2011;12:69–78.

[9] Florentina M, Antke Z, Phillipo LC, Benson RK, Mange M. Pattern and factors associated with congenital anomalies among young infants admitted at Bugando medical centre, Mwanza, Tanzania. BMC Res Notes 2014;7:195.

[10] Shabbir H, Imran A, Moin-ud-Din S, Mazhar NC, Saba HT, Rabia M. Prevalence and pattern of congenital malformations among neonates in the neonatal unit of a teaching hospital. J Pak Med Assoc 2014;64:6.

[11] Sheeba M, Sushmita S, Harpreet K, Monika G, Goraya SPS. Surveillance of congenital malformations and their possible risk factors in a teaching hospital in Punjab. Int J Reprod Contracept Obstet Gynecol 2014;3(1):162–7.

[12] Akruti P, Rathod SP, Patel SV, Patel SM. A study of congenital anomalies in newborn. NJIRM 2010;1:1.

[13] Sanghvi KP, Merchant RH, Gondhalekar A, Lulla CP, Mehta AA. Mehta KP Antenatal diagnosis of congenital renal malformations using ultrasound. J Trop Pediatr 1998;44:235–40.

[14] Jagteshwar G, Suzan LC, Wei Y, Gary MS. Paternal age and congenital malformations in offspring in california, 1989–2002. Maternal Child Health J 2012;16:385–92.

[15] McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. Epidemiology 1995;6:282–8.

[16] Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? Hum Rep 2007;22:696–701.

[17] Materna-Kiryluk A, Wis niewska K, Badura-Stronka M, Mejnartowicz J, Wieckowska B, Balcar-Boron A, et al. Parental age as a risk factor for isolated congenital malformations in a Polish population. Paediatr Perinat Epidemiol 2009;23:29–40.

[18] Gul F, Jabeen M, Khan AS. Frequency of congenital malformations and associated risk factors at Liaqat Memorial Hospital Kohat. Khyber Med Univ J 2012;4:119–24.

[19] Rittler M, Liascovich R, López-Camelo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. Am J Med Genet 2001;102:36–43.

[20] Bromiker R, Glam-Baruch M, Gofin R, Hammerman C, Amitai Y. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. Clin Genet 2004;66:36–63.

[21] Naeimeh T, Katayon Y, Nazila N. The prevalence of congenital malformations and its correlation with consanguineous marriages. Oman Med J. 2010;25.

[22] Truong H, Dung TN, Phuong VNN, Dong AT, Yves G, Raymond R, et al. External birth defects in southern Vietnam: a population-based study at the grassroots level of health care in Binh Thuan province. BMC Pediatr 2013;13:67.

[23] Prasoona KR, Srinadh B, Sunitha T, Sujatha M, Deepika MLN, Vijaya Lakshmi B, Aruna Ramaiah, Jyothy A. Seroprevalence and influence of torch infections in high risk pregnant women: a large study from South India. J Obstet Gynecol India 2015:616–8.

[24] Friedman, Polifka. Teratogenic effects of drugs. Baltimore, MD: The John Hopkins University Press; 1994. p. 616–8.