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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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KEYWORDS

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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,