East African Medical Journal Vol. 94 No. 1 January 2017
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BECKWITH-WIEDEMANN SYNDROME IN ASSISTED REPRODUCTIVE TECHNIQUES: CASE REPORT

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SUMMARY

Assisted Reproductive Techniques (ART) is a crucial treatment for infertile couples and is frequently common. ART entails manipulation of oocyte and sperm in a laboratory: *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). The key objective of ART is to yield superior quality embryos that are competent for implantation with good perinatal outcome. In spite of widespread acceptability of ART, concerns have been raised on the long-term safety of removal and manipulation of the gametes and embryos. High incidence of imprinting disorders like Beckwith-Wiedemann syndrome (BWS) have been noted in babies conceived after ART. The case report discusses BWS encountered after conception with ART and a review of other imprinting disorders associated with ART.

INTRODUCTION

ART has been associated with occurrence of congenital malformation, low birth weight babies and imprint disorders (1-4). Concerns have been raised on the association of ART and imprinting disorders (2). Beckwith-Wieldemann Syndrome, Angelman Syndrome, Russel-Silver Syndrome and maternal hypomethylation syndrome have been implicated in imprinting disorders (5-7). Evaluation of evidence of these imprinting disorders and their linkage to ART is discussed.

CASE REPORT

Thirty-two years old patient was diagnosed with secondary infertility for two years on 14/03/2014. The significant past history was spontaneous abortion on 2012 and open myomectomy on 2013.

Clinical Findings: She was in good general condition, not pale and afebrile. The significant finding was a low transverse scar and a bulky uterus.

Investigations performed: HSG: Uterine cavity was normal without filing defect. There was also bilateral tubal dye spill.

Pelvic Ultrasound: Normal uterus with a volume of 140 cubic centimeter. Both ovaries were normal.
Semenanalysis X 2: Azoospermic
Testicular Ultra sound: Normal

Hormonal Profile (Male): Testosterone – 24 ng/dl (Normal 240-950ng/dl), FSH- 14 IU/L (Normal 2-10IU/l).

A diagnosis of azoospermia with testicular failure was made.

Female Hormonal Profile:
AMH 27.8 pmol/1
Thyroid Function Test- Normal
Prolactin test - Normal
ELISA –Negative
Hepatitis B SAG-Negative

Decision made to perform ART-Intracytoplasmic Sperm Injection with testicular sperm aspiration. She had ovulation stimulation with gonadotropins from 17/04/2016 to 26/08/2016, and the oocyte retrieval on 27/08/2016. Thirteen oocytes were retrieved with development of 10 embryos. Three embryos transferred on 29/04/2016.Serum BHCG performed on 11/05/2016 was 269I.u, confirming pregnancy. The pregnancy was maintained on duphaston 10mg BD per oral and sustain 400mg pessaries Per Vaginal.

Obstetric ultrasound performed on 02/06/2016: Intrauterine pregnancy at seven weeks with a viable fetus.

Obstetric ultra sound at thirteen (13) weeks: Single live intrauterine pregnancy at thirteen (13) weeks four

(4) days. Fetal Abdominal cyst mass and renal cyst mesenteric cyst were queried.
Follow up was advised.

Obstetricultrasound was done on 16/08/2016 Gross multiple fetal anomalies were noted and included:1). Gross hydrocephalus.2). Caudal Spinal regression Syndrome.3). Gross anterior abdominal wall defect with floatingliver, bowel loops and urinary bladder. 4). Poorly uterine fetal limbs. Patient was counseled on poor prognosis and on the necessity to terminate the pregnancy. The patient was admitted at a private hospital and termination of pregnancy performed.

Fetus: On abortion the fetus was found to have gross abnormalities with ompholoecele, macroglosia and hemiplasia. A diagnosis of Beckwith-Wieldman Syndrome was made based on the above findings.

DISCUSSION

ART babies have a double risk of having major birth defects as compared to naturally conceived babies (1,2), while imprinting disorders are more prevalent in human ART cohort (3,4). Concerns have been raised on the association of ART and imprinting disorders (2). BWS, AS, RSS and maternal hypomethylation syndrome have been implicated in imprinting disorders (5-7). The baby aborted after conception with ART had BWS. Evaluation of evidence of these imprinting disorders and their linkage to ART is discussed.

Beckwith-Wiedemann Syndrome (BWS): BWS affects about 1 in 13,700 children and majority of the cases are due to epimutation of the maternal allele of one of the two differentially methylated regions (DMRs) at chromosome 11p15 (7). The syndrome has variable clinical presentations, which include large pre/post-natal growth, exomphalos, macroglosia, neonatal hypoglycaemia, hemihypertrophy, and childhood tumours, particularly wilms tumour (7). The patient presented had exomphalos, macroglosia and hemiplasia. BWS registries indicate that this syndrome has been noted in children born after ART. In the higher percentage of these patients, hypomethylation of the maternal alleles of DMR2 has been found to be the underlying molecular mechanism (7). Lim *et al* (25) and Gicquel *et al* (9), respectively, found 96% and 100% of ART children had hypomethylation at KvDMR1. Patient's with BWS with an epimutation have 14 times more probability of having undergone conception by ART than patients without epimutation BWS (10). BWS has also been documented in children born after ovulation induction (7). BWS children born of ART were found to be 10 times than the expected frequency (5). Halliday *et al* (11), found the risk of BWS in ART population was 9 times higher than in the general population while Debaun *et al* (4), reported BWS prevalence of 4.6% in ART children compared to the anticipated background rate. Several studies have found evidence showing real association between disordered imprinting causing BWS in ART (12,9,5,4,7,13,14).

Angelman syndrome (AS): AS inflicts 1 in 16,000 children and is characterised by a spectrum of genetic defects (2). Phenotypically the patient manifests withsevere mental retardation, micro-cephaly, brachycephaly, seizures, ataxic movements of the limbs and trunk and happy demeanor. Approximately 70% of AS patients have deletion of 4-6MB 15q11.2-15q13 imprinting centre (2). In AS, deprivation of methylation at the SNRPN imprinting control region has also been noted (12). ART, especially ICSI has been associated with AS (5,25). However, Vermeiden *et al* (3), in there literature review, found no association between AS and ART.

Silver-Russel Syndrome (SRS): SRS affects 1 in 100,000 children and is depicted by intrauterine and post-natal growth retardation and learning disabilities (7). Phenotypically, the patient manifests with a small body, blue sclera and high forehead that tapers to a small jaw. The most common defect is hypomethylation of H19/IGF2 at chromosome 11p15.5 (5,14). Recent study indicates that the prevalence of SRS patients in ART is 10 times greater than expected (Figure 1) (5).

Other imprinted disorders: Prader-Willi syndrome, MatUPD14 syndrome, PatUPD syndrome, Pseudohypoparathyroidism1b and Transient neonatal diabetes mellitus are not associated with ART (6). Originally, retinoblastoma was linked with ART but current data does not associate it with ART (15,5,2).

However, imprinting disorders are so infrequent that a moderate elevation after ART cannot be noticed in a sample of less than 10,000 children (13).

Relationship between ART and imprint disorders. ART/Natural, percentage of all children born due to ART were 0.86%. BWS and SRS children born of ART were found to be 10 times than expected frequency when compared to ART/ Natural.

ART, epigenetic and long-term health: Except for the documented printing disorders, transmission to the offspring of induced epigenetic variation without specific phenotypical effect can occur and may affect susceptibility to disease in later life (12,5). Hypomethylation of KCNQ10T as well as H19 has been demonstrated in chorionic villus samplings of ART patients with spontaneous abortion and stillbirth (16). The prevalence of elevated blood pressure, overweight and obesity, raised fasting blood sugars and increased risk of cardiovascular and metabolic disease have been found in IVF offspring (2). This may be linked to aberrant epigenetic.

In conclusion, in ART, the developing epigenome

is exposed to external stimuli that may interfere with appropriate establishment and maintenance of genomic imprint (14). Methylation patterns may be statistically different between ART and non-ART cohorts (16,17). Specific imprinting disorders (BWS, AS, SRS and MHS) are associated with ART (5,7,18). However, absolute risk of bearing a child with imprinting disorder after ART remains low. Manipulation of the gametes and embryos and extension of embryo culture should be minimised to avoid negative epigenetic effects (17).

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