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7 **Ovarian Hyperstimulation and Maternal Virilisation with Successful**
8 **Pregnancy Outcome**

9 *A case report*

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18
19 **Abstract**

20 Hyperreactio luteinalis (HL) and ovarian hyperstimulation syndrome (OHSS) during
21 pregnancy are both benign conditions where the ovaries are enlarged with presence of
22 multiple thin-walled cysts. Differential diagnosis is ovarian malignancy. Hyperandrogenism
23 with resultant maternal virilization could be seen in some cases of HL as well as in androgen
24 secreting tumours. We report the case of a 41 years old lady underwent ovulation induction
25 due to secondary infertility. She had recurrent hospital admission with abdominal pain and
26 huge multicystic enlargement of both ovaries. She developed virilisation features by 35
27 weeks of pregnancy. Lower segment caesarean section was done at 36 weeks gestation for
28 breech presentation with intra uterine growth restriction. Magnetic resonance imaging (MRI)
29 confirmed benign nature of the cysts. Ovarian cysts and hyperandrogenism gradually
30 resolved by three months of delivery. Awareness, judicious imaging and close monitoring in
31 such cases can result in live birth and avoid oophorectomies.

32 **Keywords:** Hyperandrogenism; Hirsutism; Virilism; Polycystic ovary syndrome; Ovarian
33 hyper stimulation; Ovulation induction; Hyperreactio luteinalis; Ovarian cysts.

34

35 **Introduction**

36 Hyperreactio luteinalis in pregnancy is a benign condition where the ovaries are enlarged
37 with presence of multiple thin walled cysts.¹ This occurs as a result of hypersensitivity of
38 ovarian tissue to human chorionic gonadotropin.¹ A similar clinical picture happens in
39 ovarian hyperstimulation syndrome (OHSS) characterised by a cystic enlargement of the
40 ovaries, associated with shifting of body fluid into third compartment, due to over production
41 of vascular endothelial growth factor (VEGF) and inflammatory factors.² Usually, it is a
42 complication of assisted reproductive technology (ART).³ Both conditions would result in
43 complicated pregnancy; preterm labour, pregnancy induced hypertension/preeclampsia and
44 intra-uterine growth restriction.^{4,5} Bilateral huge ovarian enlargement can be mistaken with
45 malignancy.⁶ This may result in oophorectomies.

46

47 Elevated serum testosterone can be physiological in pregnancy.⁷ Luteinic cysts, androgen
48 secreting tumours of adrenal and ovaries, 21 hydroxylase deficiency and Cushing syndrome
49 can cause virilisation in pregnancy.⁸

50

51 We report a case where a patient underwent ART, developed huge multicystic ovaries with
52 virilisation in pregnancy who was conservatively managed resulting in live birth and
53 preserved ovaries.

54

55 **Case report**

56 A 41-year-old lady was referred to High risk pregnancy unit in June 2022 with a viable 14
57 weeks pregnancy and bilateral large hyper stimulated ovaries. This was her fifth pregnancy.
58 She had previously three normal deliveries, all conceived with ovulation induction. She was
59 following in Fertility Clinic as secondary infertility for seven years. She was diagnosed with
60 polycystic ovarian syndrome with poor ovarian response, consuming high doses of
61 gonadotropins. Patient conceived after four cycles of letrozole with follicular stimulating
62 hormone (FSH) 150IU and human menopausal gonadotropin (HMG) 150 IU. She was started
63 on low molecular weight heparin for thromboprophylaxis, low dose aspirin and folic acid.

64

65 First trimester ultrasonography showed enlarged ovaries with multiples large thin walled
66 clear cysts, left ovary 21x18 cm, right ovary 16x13 cm. Anatomy scan at 22 weeks showed
67 no structural defects for fetus. Left ovarian size and morphology remained the same but right
68 ovary had decreased in size to 8X5 cm. (figure 1). There was no ascites.

69

70 She was admitted multiple times with abdominal pain, nausea and occasional vomiting.
71 Ascites or pleural effusion were not detected on ultrasonography. There was no evidence of
72 torsion ovary. She remained haemo-dynamically stable. Serum electrolytes,
73 aminotransferases, creatinine and haematological parameters all were within the reference
74 range. Patient was conservatively managed with analgesics, antiemetics and
75 thromboprophylaxis.

76

77 Last admission was at 35 weeks with abdominal pain. Sonographic examination revealed
78 single live breech fetus, estimated weight 1.9 kg, abdominal circumference (AC) less than 1st
79 centile, placenta was anterior high, liquor normal, umbilical artery doppler pulsatility index
80 (UAD PI) was 1.13. Both ovaries were with large multiple thin walled cysts. Right and left
81 ovary were measuring 8.5 cm and more than 15 cm respectively with normal color flow. No
82 ascites. She was planned for fetal monitoring and delivery at 37 weeks.

83

84 It was noted at this time that patient's voice was becoming hoarse and deep and there was
85 hirsutism on abdomen and chest. Serum testosterone was sent and found to be high, reaching
86 to 24mmol/l. Case was discussed with Gyne oncology team and radiologist in view of a rare
87 possibility of androgen secreting tumor. She was planned for postnatal Magnetic resonance
88 imaging in view of the late gestation and technical difficulties in proper imaging. Couple
89 were informed of the clinical situation and if MRI reveals an androgen secreting tumor, she
90 will require relaparotomy with staging.

91

92 Patient underwent elective caesarean section (CS) at 36 weeks for breech presentation and
93 abnormal doppler parameters one week after admission. A female baby, weighing 2.2 kg was
94 delivered with good Apgar score. Baby did not show any evidence of virilisation. The CS
95 was performed through a pfannensteil incision with minimum trauma to the enlarged ovaries.
96 Hence intra operative photograph could not be taken. Peritoneal washing taken during
97 cesarean section, reported later as negative for malignancy.

98

99 Magnetic resonance imaging (MRI) done 2 days post caesarean section, reported as
100 multicystic appearance of both ovaries- picture of ovarian hyperstimulation or benign cysts.
101 There is a chance that using USS alone as an imaging modality might miss a small solid
102 lesion in a huge ovary in a postpartum patient with thick abdominal wall and enlarged uterus.
103 Hence MRI was performed as discussed with Gyne oncologist and consultant radiologist.
104 Left ovary measuring 15x10cm, the largest cyst measures 11x10cm showing thin wall and no
105 solid enhancement and no diffusion restriction. Right ovary measures 6x7cm with multiple
106 cysts, the largest measures 3.2x3cm and shows irregular wall, however there was no solid
107 enhancement or diffusion restriction.(Figure 2) She underwent computerized tomography
108 (CT) examination of chest, abdomen and pelvis also which did not reveal any significant
109 abnormality other than bilateral cystically enlarged ovaries.(Figure 3,4). Endometrial cavity
110 is distended in both CT and MR images due to post-partum status.

111

112 Patient and baby were discharged well on 5th postoperative day. After two months she was
113 reviewed in gyne-endocrine clinic. Her investigations revealed a drop in serum testosterone
114 to 11mmol/l.17-hydroxyprogesterone was 18.1mmol/l, alpha fetoprotein was 108ug/l and
115 other tumor markers were all within normal range. Transvaginal sonography revealed thin
116 endometrium, left ovary with large cyst 8x10cm, right ovary normal. She was followed for 6
117 months postpartum. Testosterone levels came down to normal. Growth hormone, IGF -1 and
118 dexamethasone suppression test, Thyroid function test, HbA1C were normal. Her last follow
119 up on March 15th, 2023, showed further regression of bilateral cysts.

120

121 Patient consent was obtained for clinical photography and publication of case report.

122

123 **Discussion**

124 Ovarian hyperstimulation syndrome is an iatrogenic complication of assisted reproductive
125 technology cycles, estimated around 20% to 33% in its mild form and 3% to 8% in its
126 moderate or severe form.⁹ Risk factors of developing OHSS are age less than 35 years, low
127 body weight, hypothyroidism, ovulation stimulation protocols, high estradiol levels, rapid
128 elevation in estradiol levels, number of the stimulated follicles, number of the removed
129 oocytes, pregnancy, and the presence of polycystic ovaries.^{10,11} According to Royal college of
130 obstetricians and gynaecologists (RCOG) classifications of OHSS severity; in severe cases,
131 ovarian size usually > 12 cm and associated with fluid shift to third space and biochemical
132 abnormalities.¹² Hyperreactio luteinalis (HL) is a benign bilateral cystic enlargement of the

133 ovaries, due to ovarian stimulation by Beta Human chorionic Gonadotropin(Beta hCG) in
134 spontaneous Cycles.¹³ Our patient presented in first trimester with background of ART with
135 bilateral huge multicystic ovaries. She was diagnosed initially as OHSS even though she had
136 none of the other risk factors for OHSS mentioned above. In spite of recurrent admissions
137 with abdominal pain, she never had biochemical abnormalities or fluid shift to third space
138 which pointed towards the alternative diagnosis of hyperreactioluteinosis (HL). The cause of
139 her ovarian multicystic enlargement may not have been due to hormonal treatment, but a
140 hypersensitivity of ovarian stroma to hCG which is said to be the cause of HL.¹⁴ HL usually
141 manifest in primigravida, present in second and third trimester in spontaneously conceived
142 pregnancy.¹⁴ Risk factors include gestational trophoblastic disease, multiple pregnancies and
143 chronic kidney diseases and hypothyroidism. Most of the patients are asymptomatic, and it is
144 incidentally discovered during routine ultrasound examination or during Caesarean section.¹⁴
145 Some patients reported abdominal pain due to ovarian torsion or haemorrhage.^{1,13} Our patient
146 did not have any of the risk factors for HL mentioned above. There was no feature of torsion
147 or haemorrhage in any of her admissions. As the ovarian cysts were considered benign by
148 their ultrasound appearance, and as no cyst accidents happened, she was conservatively
149 followed. The ultrasound image provided is suboptimal due to abdominal wall obesity,
150 gravid uterus, huge ovarian enlargement.

151

152 Hyperandrogenism is a normal physiological change in pregnancy due to increase
153 testosterone production by human Chorionic Gonadotrophin (hCG) stimulation, adrenal
154 influence and reduced renal clearance of testosterone.⁸ Maternal virilization is rare, as
155 protective mechanisms like increased serum sex hormone binding globulin in pregnancy and
156 placental aromatase conversion of androgen to estrogen reduce excess androgen exposure in
157 the mother and the foetus.^{13,15} Maternal virilization is reported in 20-30% of cases of HL due
158 to severe hyperandrogenism.¹ Virilisation is rarely seen in OHSS.⁶ Our patient was noted to
159 have features of virilisation by 35 weeks of pregnancy. Even though the sonological
160 morphology of ovarian cyst looked benign, she was planned for postnatal MRI to rule out the
161 rare possibility of an androgen secreting tumour.

162

163 Cavoretto P et.al,⁵ has done an extensive review compiling 96 cases of HL reported from
164 1955 to 2013. They have reported preeclampsia in 24 % and fetal growth restriction in 12 %
165 of cases. Mean gestation at delivery was 35 weeks. Oophorectomy was reported in 40 % in
166 this group. Pregnancies complicated by HL is reported to have higher incidence of pre-

167 eclampsia, growth restriction and preterm delivery.¹⁶ This is attributed to the elevated beta
168 HCG levels seen in HL.^{14,16} Our patient was delivered by LSCS at 36 weeks due to breech
169 presentation with intrauterine growth restriction and abnormal dopplers. Exposure to high
170 androgen levels after 12 weeks of pregnancy may not produce virilisation in female foetuses
171 as seen in our case. Placental aromatisation of androgens as well as increased fetal exposure
172 to estrogens may offer protection to fetus from maternal androgens.^{14,17} We did not encounter
173 failure of lactation which is reported in women with high androgen levels.¹⁷

174

175 Our patient had postnatal imaging which ruled out androgen secreting tumour. She was
176 followed up in combined Gyne endocrine clinic which revealed spontaneous regression of
177 ovaries as well as resolution of hyperandrogenism.

178

179 **Conclusion**

180 In summary, we report a unique case with showed mixed picture of OHSS & HL. Both
181 diagnoses shared same ultrasonographic appearance. Conservative approach is used to
182 manage both conditions, reserving surgical intervention for cyst accidents. Pregnancy can be
183 continued to term unless maternal or fetal complications occurred. In case of maternal
184 virilisation, ovarian androgen secreting tumours as well as other pathologies to be ruled out.
185 Awareness of the pathology, ultrasound features, judicious imaging, close fetomaternal
186 monitoring can lead to successful pregnancy outcome as well as avoid oophorectomy.

187

188 **Authors' Contribution**

189 JS and TR managed the case. Endocrinology follow-up was carried out by MSS and NRH.
190 JK and MSSH analysed the radiological data. ISHG drafted the manuscript. All authors
191 critically reviewed the manuscript and approved the final version of the manuscript.

192

193 **Acknowledgement**

194 We acknowledge the support of the Royal hospital doctors and staff in the clinical
195 management of the case.

196

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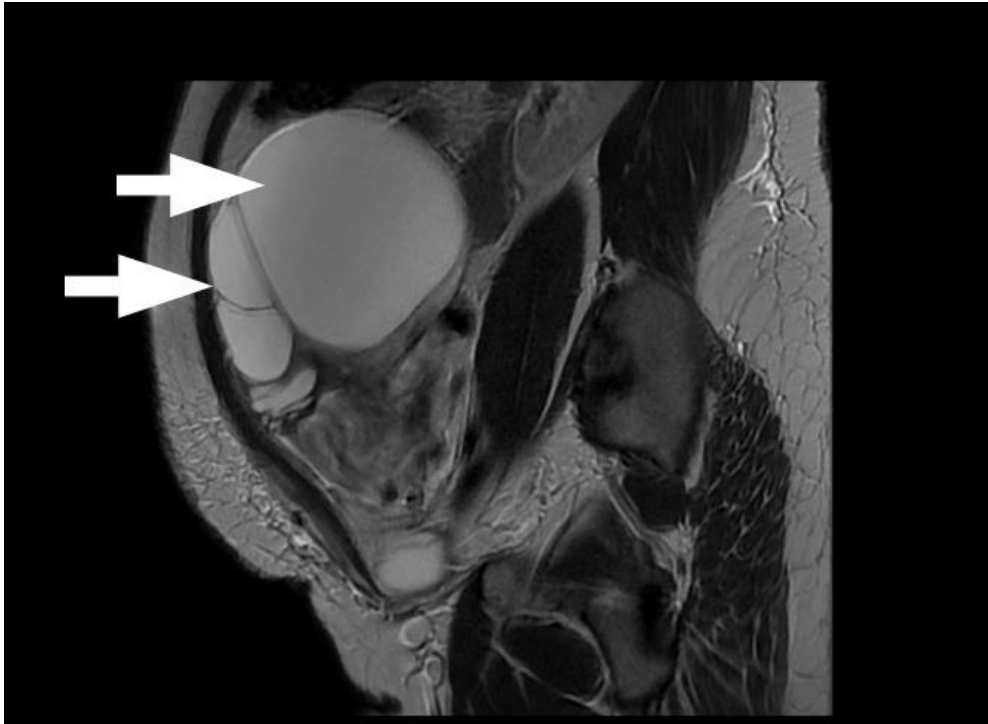
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262 **Figure1:** Ultrasound scan showing bilateral large ovarian cysts

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264

265 **Figure 2:** MRI Axial T2 weighted image showing simple looking cysts in ovary

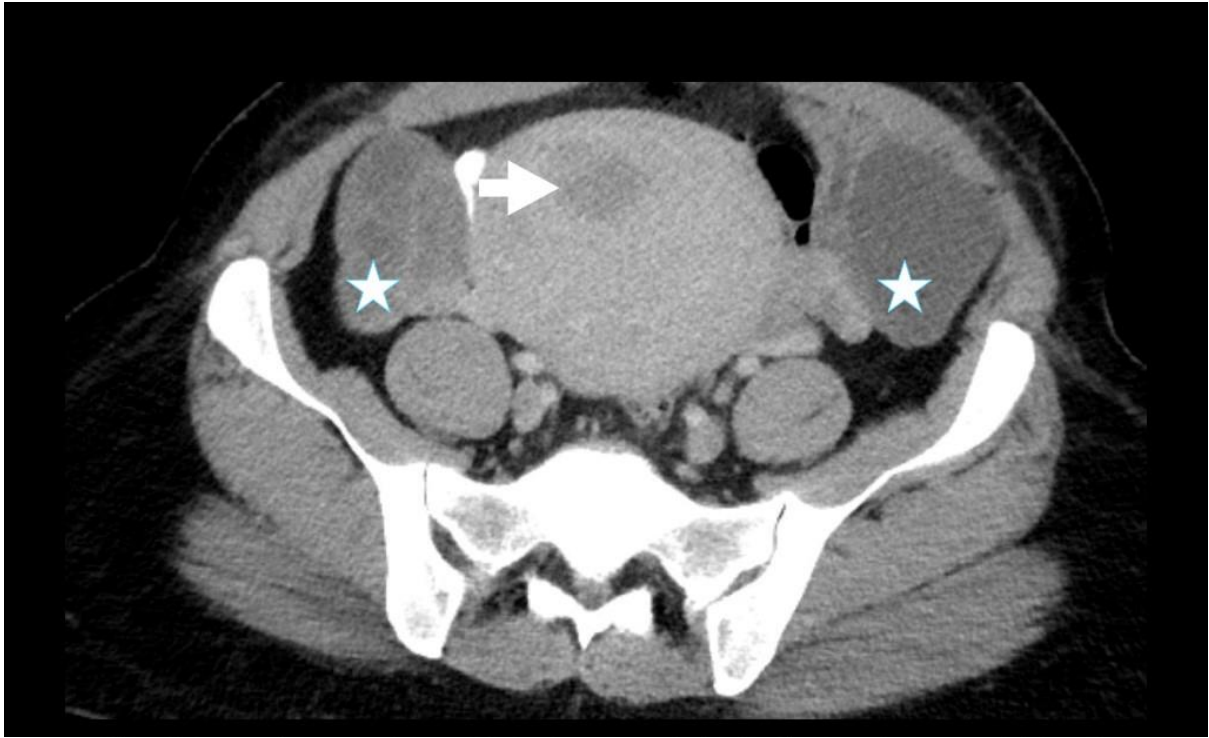
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268 **Figure 3:** CT Axial image with contrast showing bilateral ovarian cyst

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270

271 **Figure 4:** CT Axial image with contrast showing bilateral ovarian cyst