Fertility in McCune Albright syndrome female: A case study focusing on AMH as a marker of ovarian dysfunction and systematic review

Agopiantz M[a,b,*], Sorlin A[c,d], Vabres P[d,e], Guillet-May F[a], Bonnet C[b,c], Koscinski I[b,f], Gauchotte G[b,g].

[a] Department of Gynecology and Obstetrics, CHRU de Nancy, Université de Lorraine, Nancy, France ; [b] INSERM U1256, Université de Lorraine, Vandœuvre-lès-Nancy, France ; [c] Department of Genetics, CHRU de Nancy, Université de Lorraine, Vandœuvre-lès-Nancy, France ; [d] EA 4271, Université de Bourgogne Franche-Comté, Dijon, France ; [e] Department of Dermatology, CHU de Dijon, Université de Bourgogne Franche-Comté, Dijon, France ; [f] Department of Biology of Reproduction, CHRU de Nancy, Université de Lorraine, Nancy, France ; [g] Department of Pathology, CHRU de Nancy, Université de Lorraine, Nancy, France.

Background: The molecular basis of McCune Albright syndrome (MAS) is a recurrent postzygotic gain of function sporadic mutation of *GNAS*, resulting in a mosaic disease. Most of girls present precocious puberty, caused by the development of recurrent ovarian cysts with autonomous hyperestrogenic stimulation. After menarche most of the patients with ovarian *GNAS* mutation have menstrual disturbances and infertility.

Objectives: We wanted to focus on the fertility of MAS females and propose an appropriate management, by a detailed case report and an exhaustive review of the literature on fertility and pregnancy in MAS females.

Table 1 - Oocytes evaluation and embryonic development.

Oocyte	Morphology	ICSI	24 h	48h	Issue
1 PB	Thick ZP / D	+	Lysis	-	-
1 PB	Thick ZP / PB fragmentation / D	+	2 PN	4 A F > 50%	Frozen at day 5 (B4 B C)
Lysis	-	-	-	-	-
1 PB	GC / Thick ZP	+	1 PN	3 A F > 50%	Lysis at day 5
1 PB	GC / Large PS / D	+	2 PN	2 T F=25%	Transferred at day 2
1 PB	GC / Large PS / D	+	Lysis	-	-
1 PB	GC / Large PS / PB fragmentation / D	+	2 PN	2 A F=25%	Frozen at day 2
1 PB	GC / Irregular ZP	+	1 PN	Lysis	-

PB: polar body; ZP: zona pellucida; D: debris; GC: granulous cytoplasm; PS: perivitelline space; PN: pronucleus; F: fragmentation; A: atypical; T: typical.

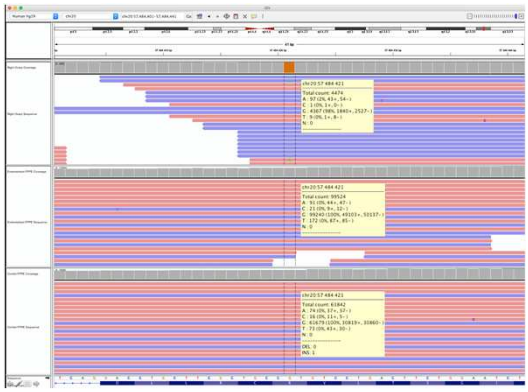

Figure 1 - Integrative Genomics Viewer screenshot of targeted deep sequencing of exon 8 of *GNAS*. The chr20:g.57484421G>A mutation (NM_000516.5:c.602G>A, p.(Arg201His)) was found in 97 of the 4473 reads at this position (2.17%). No mutation was found in endometrial tissues.

Results:

- We present the case of a 29-year-old MAS female, who had previously undergone an unilateral ovariectomy and was managed by *in vitro* fertilization (IVF).
- Eight oocytes with many morphological abnormalities were retrieved after high doses stimulation (Table 1).
- The *GNAS* mutation was found at a low frequency (2%) in follicular cells, but not in the endometrium nor in blood (Figure 1).
- Ovarian histopathological examination showed developing follicles of any stage (Figure 2), strongly expressing AMH by immunohistochemistry (Figure 3).
- In addition, AMH was high (45.5 pmol/L) and the AMH / AFC ratio (5.69 pmol/L per follicle) was much higher than in PCOS and control patients (2.16, and 1.34 respectively) (Table 2).

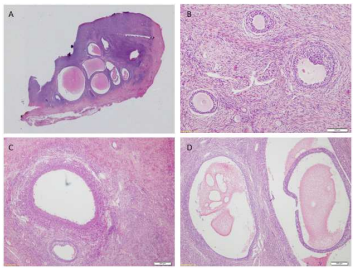

Figure 2 - Microscopic evaluation of 4-year old McCune Albright *GNAS* mutated ovary (HES coloration). Presence of all stages of follicular development (A, x10). Primordial and primary follicles in the ovarian cortex (B, x100). Primary and secondary follicles (C, x40). Large non-luteinized follicles (D, x40).

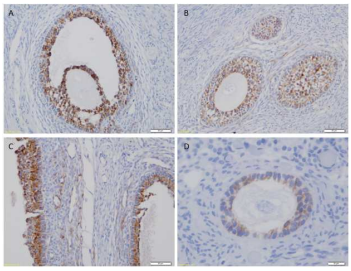

Figure 3 - Immunohistochemical staining for AMH in McCune Albright ovary. Strong cytoplasmic and granulous staining in granulosa cells of a secondary follicle (A, x200). Moderate staining in primary follicles (B, x200). Strong staining in a large-sized follicle (C, x200). Weak AMH expression in a control ovarian primary follicle (D, x400).

Table 2 - Comparison of baseline demographic, clinical, and AMH/AFC ratio in the MAS patient, PCOS, and control groups.

Variable	MAS (n=1)	PCOS (n=54)	Control (n=124)	*p value*
AMH (pmol/L)	**45.5**	65.6 ± 38.2	20.3 ± 14.3	*p<0.001*
CFA	**8**	35.1 ± 17.9	16.5 ± 8.6	*p<0.001*
AMH/AFC ratio	**5.69**	2.16 ± 1.46	1.34 ± 0.93	*p=0.001*
Age (year)	**29**	28.6 ± 3.8	29.7 ± 3.9	*NS*
BMI (kg/m2)	**29.7**	27.9 ± 6.7	24.5 ± 4.9	*p=0.001*
Smoking	**0/1**	15.1%	22.1%	*NS*
Secondary infertility	**0/1**	11.3%	20.2%	*NS*

AMH: antimullerian hormone; AFC: antral follicle count; MAS: McCune Albright syndrome; PCOS: polycystic ovarian syndrome. Mann-Whitney U test and chi-2 test. Results are expressed as mean value ± standard error mean or n (%). P values are expressed for PCOS vs. Control.

Discussion: Ovarian and endometrial involvement can be responsible for infertility in MAS women. IVF and oophorectomy may be useful in management (Table 3). The genetic characterization of the different tissues may have a prognostic utility. Moreover, we propose the AMH as a marker of the ovarian activity of MAS. Further studies are needed to clarify the potential oocyte abnormalities and the risk of miscarriages in order to guide genetic counseling (Table 4).

Table 3 - Potential risks for fertility, etiology and proposed management in McCune Albright syndrome females.

Potential risk	Etiology	Management
Anovulation	Ovarian cysts	Unilateral oophorectomy
	Multiple dominant follicles	Ovarian stimulation
		IVF
Oocyte quality	*GNAS* mutation in granulosa cells	Search for mutation in follicular cells (if IVF)
Implantation capacity	*GNAS* mutation in endometrium	Search for mutation in endometrium
	Endometrial hyperplasia / Adenomyosis	Progestin treatment
Miscarriage / Stillbirth	*GNAS* mutation in oocyte (lethality)	Preimplantation genetic diagnosis (PGD)
		Genetic counseling

Table 4 - Pregnancy in McCune Albright syndrome in the literature (all cases reported).

Reference	Patients (n)	Age	Cycles	Ovarian Mutation	Infertility	Management	Pregnancy (n)	Issue	Birth weight
Lee et al.(1986)	2 (/4)	NA	Ovulatory	NA	No	Spontaneous	NA	NA	NA
Kaplan et al.(1988)	1	31	NA	NA	No	NA	1	Vaginal delivery at 38 WP	3200g
						NA	1	Early miscarriage	NA
Meinhoff et al. (1994)	1	25	NA	NA	NA	NA	1	Delivery	NA
Obuchie et al.(2001)	1	36	Anovulatory	NA	Yes (4 years)	Ovarian stimulation / IUI	1	Vaginal delivery	2590g
						Spontaneous	2	Early miscarriages	NC
Lawin et al. (2004)	1	22	Ovulatory (after oophorectomy)	Yes (unilateral)	Yes (4 years)	Oophorectomy	1	Vaginal delivery at 38 WP	3880g
Osada et al.(2005)	2	33	NA	NA	NA	Spontaneous	1	Cesarean delivery at 37 WP	2868g
					NA	Spontaneous	2	Elective abortions	NC
		26	NA	NA	NA	Spontaneous	1	Vaginal delivery at 38 WP	2402g
Kanazawa et al.(2009)	1	38	NA	NA	NA	Spontaneous	1	Cesarean delivery at 37 WP	NA
Chanson et al. (2010)	1 (/8)	22	Ovulatory (after oophorectomy)	Yes (unilateral)	Yes	Oophorectomy	2	Vaginal delivery	NA
	3 (/8)	NA	Ovulatory	NA	NA	Spontaneous	NA	NA	NA
Chevalier et al. (2015)	1	22	Ovulatory (after oophorectomy)	Yes (unilateral)	Yes	Oophorectomy / IVF	1	Stillbirth at 4 months	NC
Agopiantz et al. (2016)	1 (/5)	18	Ovulatory	NA	No	Spontaneous	1	Vaginal delivery	NA
Wong et al. (2017)	2 (/9)	NA	NA	NA	NA	Spontaneous	NA	NA	NA

IUI: intrauterine insemination; IVF: in vitro fertilization; WP: week of pregnancy; NA: not available; NC: not concerned.