

Reduced Ovarian Reserve

Is there any hope for a bad egg?

Dr. Phil Boyle

Galway Clinic, 19th March 2014

For more information on Low AMH see www.napro.ie

Anti Mullerian Hormone

- AMH levels are commonly measured in fertility clinics to assess ovarian reserve and give an indication of female fertility potential.
- AMH levels are useful in deciding on stimulation protocols for IVF cycles.
- High AMH levels are useful to confirm a diagnosis of polycystic ovaries.
- Currently AMH levels ***can not*** be used to predict a couple's ability to conceive naturally.

Bhide, P., The role of anti-müllerian hormone as a predictor of ovarian function.

[The Obstetrician and Gynaecologist](#). July 2012 Volume 14, Issue 3, pages 161–166

Anti Mullerian Hormone

AMH

- Produced by small follicles 5-7mm
- Levels indicate size of antral follicle pool
- Useful to predict ovarian response to stimulation
- Can tailor treatment to individual for IVF cycles

Bhide, P., The role of anti-müllerian hormone as a predictor of ovarian function.

[The Obstetrician and Gynaecologist.](#) July 2012 Volume 14, Issue 3, pages 161–166

Anti Mullerian Hormone

A rise in age related subfertility

Poor ART outcomes with

Advanced age

Reduced ovarian volume

Reduced antral follicle count

Elevated FSH

Reduced AMH – since 2005

Anti Mullerian Hormone

AMH levels

Constant through cycle

Decline in

pregnancy

Hormonal contraception – over 1 year use

GNRH use - zoladex

Anti Mullerian Hormone

AMH Assay

Results can be reported in pmol/l or ng/ml

The conversion factor is $1 \text{ pmol/l} = 7.14 \text{ ng/ml}$

Therefore if AMH is 1 it could be as high as

1 pmol/l which is equal to 7.14 ng/ml

Check the reference range for your lab before interpreting a result!

Anti Mullerian Hormone

- **Low levels**

 - Low antral follicle pool
 - Reduced ovarian reserve
- **High Levels**
 - PCOD

Anti Mullerian Hormone

- **Reduced Ovarian Reserve**

- Age
- Blood
 - FSH >10 iu, Oestradiol, Inhibin B, AMH
- Ultrasound
 - Ovarian Volume < 3cm², Antral Follicle count < 3
- Challenge tests

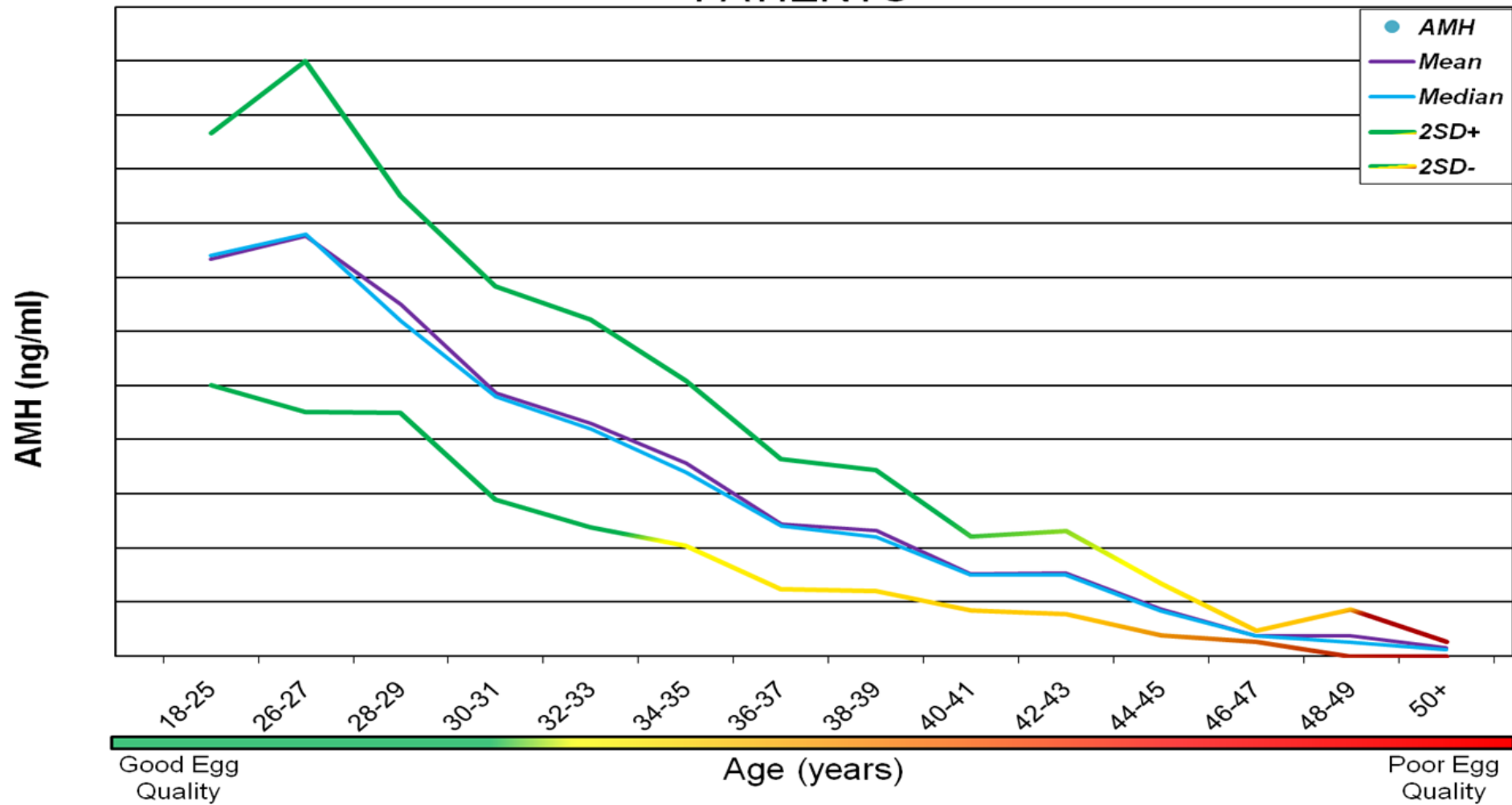
Anti Mullerian Hormone

- **AMH**

- **Age Normogram**

- Wide variation at individual ages
- Influenced by race and BMI
- Needs validation – cannot be used in clinical practice

AGE ADJUSTED AMH LEVELS FOR INFERTILITY PATIENTS



USE with caution – cannot predict ability to conceive or onset of menopause

Anti Mullerian Hormone

- **AMH Studies**

- Are in IVF Population
- Cannot predict ability to conceive naturally
- Cannot predict the age of menopause
- **BUT** extremely low levels are considered a reliable guide

Anti Mullerian Hormone

- **AMH**

- Main value is in IVF – adjusting stimulation protocols
- Role in natural conception still needs to be clarified – but it shows potential that it may be helpful in the future

Low AMH and natural conception

- Commonly women with low AMH levels are advised to consider donor eggs through IVF, with minimal attempt at natural conception.
- This paper attempts to show that ovarian stimulation with natural conception is a reasonable option to consider for women with low AMH.

Materials and Method

- Three cases of couples with low AMH, who were previously advised that their best option for conception was with donor eggs through IVF.
- Couple 1 - AMH levels 0.07pmol/l (0.0098ng/ml)
- Couple 2 - AMH levels 3.2pmol/l (0.45ng/ml)
- Couple 3 - AMH levels 2.8pmol/l (0.39ng/ml)

Couple 1 - AMH levels 0.07pmol/l

- Gravida 0, Para 0. Female and male aged 36 years old. Previous FSH 45iu/l on day 9 of cycle. AMH 0.07pmol/l, (Medlab) in June 2011. Previously advised not suitable for IVF or ICSI.
- Advised HRT, Donor Eggs and IVF.
- Intercourse without contraception since June 2006 – 6 years. Cycles irregular 26-47 days. No previous semen analysis or Laparoscopy.

IMMUNOLOGY

Anti-Mullerian Hormone

* 0.07

pmol/l

Ovarian Fertility Potential:

Optimal Fertility : 40.04 - 67.9 pmol/l

~ Satisfactory Fertility: 21.98 - 40.03 pmol/l

~ Low Fertility : 3.08 - 21.97 pmol/l

~ Very low/ Undetectable: 0.0 - 3.07 pmol/l

~ Levels greater than 67.9 pmol/l are suggestive of Polycystic Ovarian Disease or Granulosa cell tumours.

Please note change in methodology to the AMH 2nd Generation assay w/e from 06/09/2010. Values are expected to be 40% higher than those obtained previously. For comparison between 1st and 2nd Generation assays, results should be multiplied by 1.4.

Couple 1 - AMH levels 0.07pmol/l

- First consultation Galway Clinic June 2012.
- Repeat FSH on day 3 of cycle - FSH 24.8 IU, LH 6.7 IU, Oestradiol 58 pmol/l
- Record markers of fertility with Creighton Model FertilityCare Chart (Standardised Billings)
- Supplements with vitamin D3, omega 3 and folic acid and Dietary strategy
- Semen analysis

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
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	10/5	11/5	12/5	13/5	14/5	15/5	16/5	17/5	18/5	19/5	20/5	21/5	22/5	23/5	24/5	25/5	26/5	27/5	28/5	29/5	30/5	31/5	1/6	2/6	3/6	4/6	5/6	6/6	7/6	8/6	9/6					
M	M	M	VL			VVL	VVL	VVL	VVL	VVL			BC x1	10K x3	10K x3	10K x3	8C x3	8C x3	6C x3	2/6 x3	2/6 x3	6C x3	2AD	2AD	2AD	2AD	6C x3	6C x3								
			OAD	OAD	OAD	OAD	BE OAD	OAD	OAD	OAD	OAD	OAD		1"	1"	1"													OAD	OAD	OAD					
OB																																				
	10/6	11/6																																		
M	M	M																																		

Treatment Plan

Letrozole 2.5mg – 10 tabs day 3

HCG 10,000 iu mid cycle

prednisolone 5mg mane

naltrexone 3mg nocte

Ultrasound follicle tracking to monitor follicle development and rupture

Blood test on day 7 after ovulation for progesterone and oestradiol

Couple 1 - AMH levels 0.07pmol/l

- Result – Conceived on first cycle of ovulation induction, second cycle of charting.
- Pregnancy Consultation – August 2012

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35		
				👶	👶						👶	👶	👶	👶	👶	👶	👶	👶	👶	👶	👶	👶	7				👶	👶	👶								
	10/5	11/5	12/5	13/5	14/5	15/5	16/5	17/5	18/5	19/5	20/5	21/5	22/5	23/5	24/5	25/5	26/5	27/5	28/5	29/5	30/5	31/5	(1/6)	2/6	3/6	4/6	5/6	6/6	7/6	8/6	9/6						
	M	M	VL			VVL	VVL	VVL	VVL	VVL			8C x1	10CK x3	10K x3	10K x3	8C x3	8C x3	6C x3	26 x3	26 x3	26 x3	2AD	2AD	2AD	2AD	6C x3	6C x3									
			OAD	OAD	OAD	OAD	BE	OAD	OAD	OAD	OAD	OAD		1"	1"	1"														OAD	OAD	OAD					
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	10/6	11/6	12/6	13/6	14/6	15/6	16/6	17/6	18/6	19/6	20/6	21/6	22/6	23/6	24/6	25/6	26/6	27/6	28/6	29/6	30/6	31/6	1/7	2/7	3/7	4/7	5/7	6/7	7/7	8/7	9/7	10/7	11/7	12/7	13/7	14/7	
	M	M	M	M	VL	VVL	VVL	VVL	VVL	VVL	VVL			10CK x3	10K x3	10K x3	8C x3	8C x3	8C x3	6C x3	26 x3	26 x3	OAD	OAD	OAD	26-1 AD	26-1 AD	26-1 AD	26-1 AD	26-1 AD	26-1 AD	26-1 AD	26-1 AD				
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- Positive Foetal Heart
- CRL = 14.8mm ,
7weeks and 6 days
- EDD 22nd March 2013

Couple 1 - AMH levels 0.07pmol/l

- Monitored progesterone and oestradiol during pregnancy
 - Cycogest 400mg pv twice daily – Stopped at 24 weeks
 - Fematab 2mg bd po twice daily – Stopped at 24 weeks
 - Naltrexone 3mg nocte – stopped at 20 weeks
 - Prednisolone 5mg mane – stopped at 28 weeks
 - Supplements – Vitamin D3 - Stopped at 38 weeks

Couple 1 - AMH levels 0.07pmol/l

- Vaginal delivery with Forceps.
- Full term - 22nd March 2013
- Birth Weight 9lbs – 0 oz. (4.082 KG)
- Complications - None



Couple 2 - AMH levels 3.2pmol/l

- Presented in May 2012
- History Gravida 1 Para 0. Female 35 years. Male 36 years.
- Intercourse without contraception for 5 years, since June 2007.
- Laparoscopy – Mild endometriosis 2009. Hysteroscopy normal Nov 2011.
- Semen analysis normal. Day 3 bloods and clotting studies normal. AMH 3.2 pmol/l.
- 4 cycles of IVF – 3 stimulated cycles and 1 donor egg cycle in Czech Republic – all unsuccessful.

Couple 2 - AMH levels 3.2pmol/l

- Repeat FSH on day 3 of cycle
- Record markers of fertility with CrMS.
- Naltrexone 4.5mg nocte for clinical endorphin deficiency
- Supplements
 - Vitamin D3, Omega 3, ALA, Vit. C, folic acid and Dietary strategy
- Blood test on day 7 after ovulation for progesterone and oestradiol

Couple 2 - AMH levels 3.2pmol/l

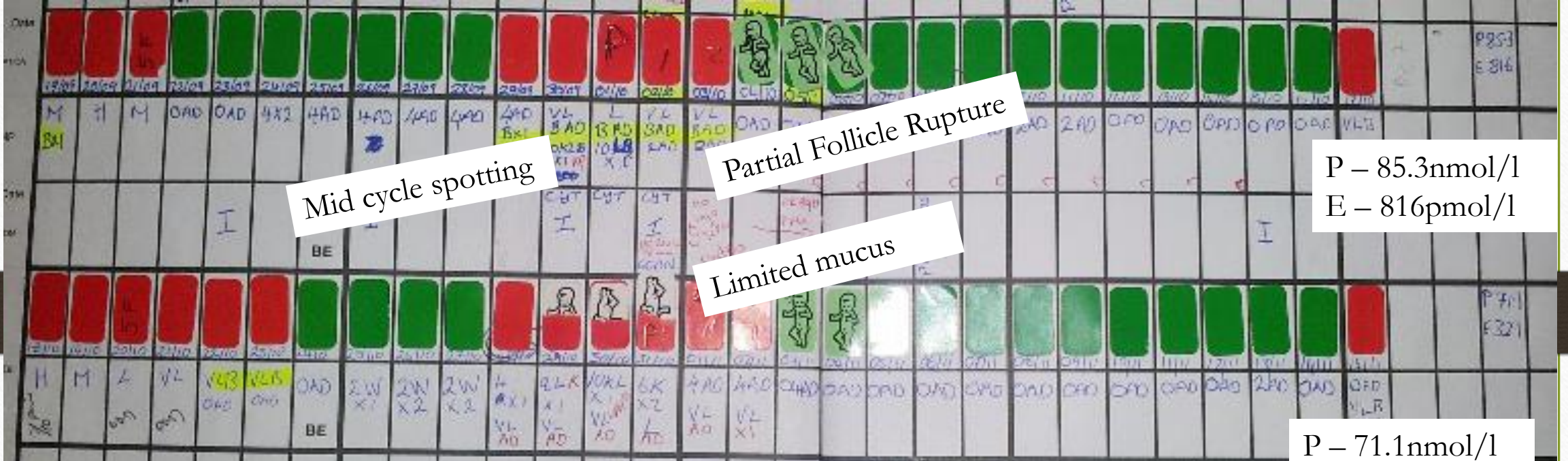
- Results
 - Day 3 bloods normal - FSH 4.6 IU, LH 3.0 IU,
 - Creighton Model FertilityCare Chart – Brown menstrual bleeding
 - Suboptimal levels of progesterone 36.7 nmol/l, - on day 7 after ovulation
 - Normal oestradiol 618 pmol/l

Couple 2 - AMH levels 3.2pmol/l

- Initial Treatment
 - Letrozole 2.5mg – 5 tabs on day 3 of cycle
 - HCG 10,000 iu – 19 mm follicle
 - Cyclogest 400mg pv nocte x 10 nights on day 3 after ovulation

Couple 2 - AMH levels 3.2pmol/l

- Results
- Fertility Chart
 - Limited cervical mucus flow
 - Mid cycle spotting
- Ultrasound Follicle Tracking
 - Partial –incomplete rupture



Mid cycle spotting

Partial Follicle Rupture

Limited mucus

P – 85.3nmol/l
E – 816pmol/l

P – 71.1nmol/l
E – 329pmol/l

Couple 2 - AMH levels 3.2pmol/l

- Adjusted treatment
 - Clomiphene 50mg daily x 5 days from day 3 of cycle
 - HCG 15,000 iu – 19mm follicle
 - Cytotec 200mcg nocte for 5 days from day 11 of cycle
 - DHEA 25mg tid x 30 days
- Ultrasound follicle tracking confirmed rupture of 2 follicles.



Improved mucus

Complete rupture 2 follicles

P – 188.7nmol/l
E – 3126 pmol/l



Improved mucus

Positive test

Complete rupture 2 follicles

P – 188.7nmol/l
E – 3126 pmol/l

Couple 2 - AMH levels 3.2pmol/l

- Pregnancy Consultation
 - Positive Foetal Heart 153 /min
 - CRL = 11mm , 7weeks and 2 days
 - EDD 21st August 2013

Couple 2 - AMH levels 3.2pmol/l

- Treatment during Pregnancy
 - Cycogest 400mg pv twice daily – ongoing
 - Fematab 2mg po twice daily – ongoing
 - Prednisolone 25mg mane – until 12 weeks, continue 5mg mane until 28 weeks
 - Naltrexone 4.5mg nocte – to stop at 38 weeks
 - Supplements – Vitamin D3 to stop at 38 weeks

Blood date	Gestation	Prog nmo	Prog ng/n	Oestradiol
14-12-2012	P+17	232.4	73.08	3484
18-12-2012		122.2	38.43	3035
08-01-2013	7w6d	88.1	27.70	1395.1
23-01-2013	10wks	91.9	28.90	1140
04-02-2013	12wks	81.6	25.66	1637
19-02-2013	13w6d	105.3	33.11	2728
13-03-2013	17 weeks	80.8	25.41	8722
27-03-2013	19wks			
09-04-2013	21wks	98.6	31.01	13870

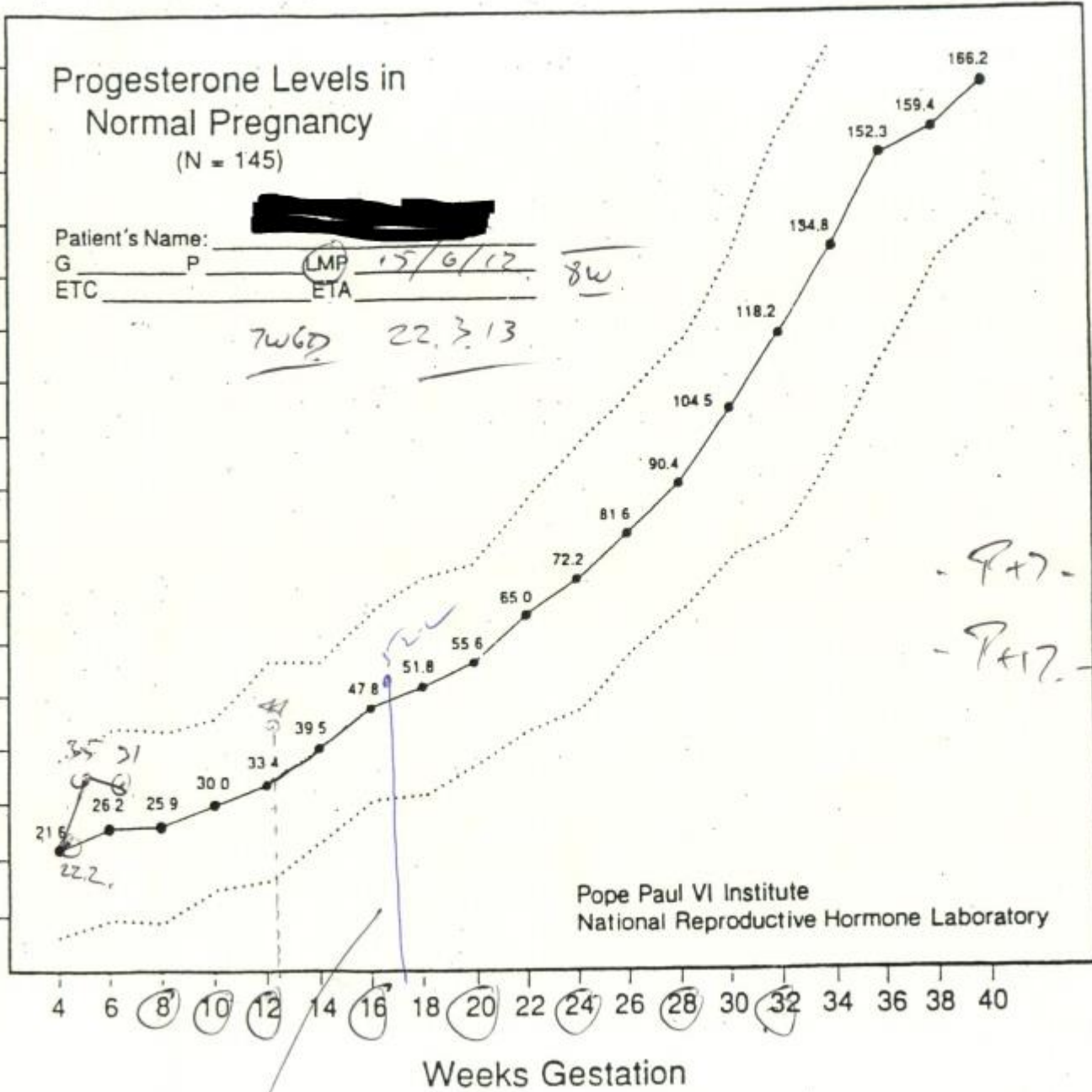
Progesterone Level (ng/ml)

Progesterone Levels in Normal Pregnancy (N = 145)

Patient's Name: [REDACTED]
G _____ P _____ LMP 15/6/12 8w
ETC _____ ETA

7w6d 22.3.13

3.18



10F D3,

CyL BD
F. ToL BD
Pled 5 on
LON 3y more

P+7 - N/A (P+3)
P-22.8
E-79.
P+17 - P 70
E 331
h 578

Weeks Gestation

Couple 2 - AMH levels 3.2pmol/l

Male or Female	Male
Birth Weight	7lb 12 oz
Actual Date of Birth	19-08-2013
Estimated date of delivery	21-08-2013
Weeks of Pregnancy	40
Delivery Details	C-Section ▼
Weeks of Progesterone Support during Pregnancy	36

After years of failed IVF, Hector was born

Niamh and Hector Hughes

NIAMH HUGHES (37) is from Castlebar and lives in Carrick-on-Shannon with her secondary school teacher husband, Daithi Hughes, and six-month-old baby son, Hector. She is currently on unpaid maternity leave from her local authority position.

"Daithi and I have been together since we met 16 years ago at college. We got married after nine years in 2007, and took a year out to travel around the world in 2000 and again in 2005. Our plan was always to have babies, so once we got married in 2007, it was the first item on the agenda.

"However, as time passed we realised it wasn't as easy as we thought it would be. Following over five years of failed IVFs and heart-breaking losses, we decided to give NaPro Technology (Galway Clinic) a go, as a last-ditch attempt before we closed that chapter of our lives.

"Symptoms that had been overlooked by conventional fertility clinics were identified and treated, and within six months I was pregnant. Getting pregnant was only the start, however. Keeping the baby in there was the hard part.

"Nerve-racking months followed. Medication



Niamh Hughes and her son Hector (six months). Photo by Brian Farrell.

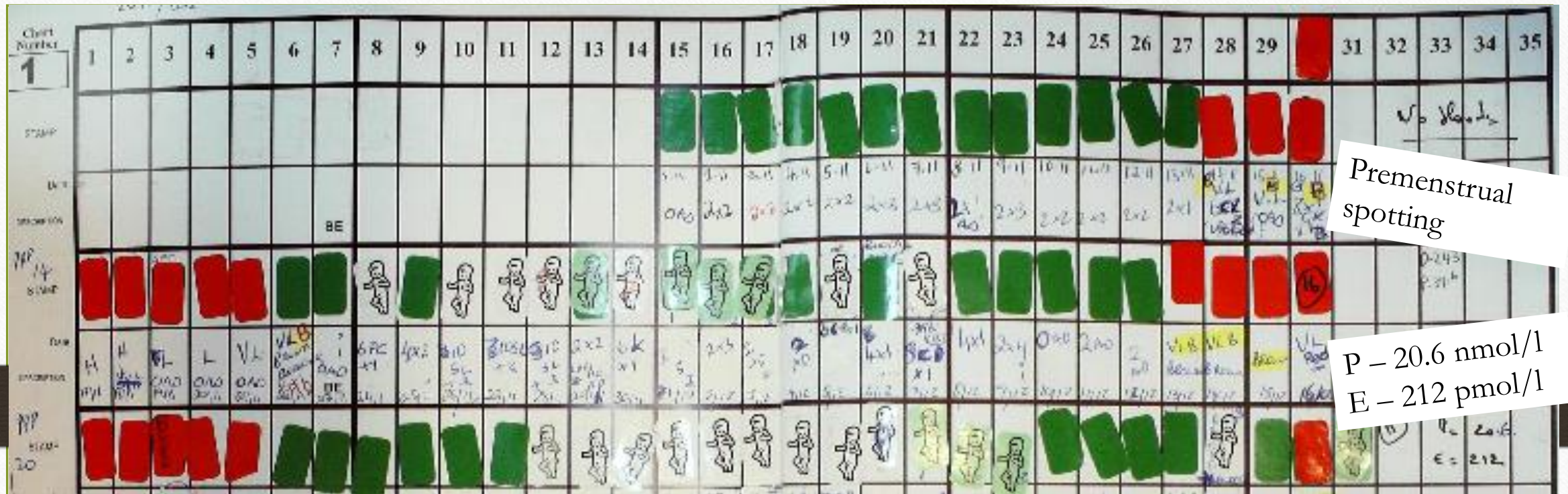
Irish Independent 24th Feb 2014

Couple 3 - AMH levels 2.8pmol/l

- Presented in Nov 2011
- **History** Gravida 1, para 1. Female 36 years. Male 46 years. First pregnancy occurred after 12 months trying. Live birth in Aug 2007. Forceps delivery, 3rd degree tear.
- Trying since Jan 2008. - Nearly 4 years. Cycle 28-34 days. Laparoscopy Apr 2010 – normal. Semen analysis normal. Routine bloods normal . Ultrasound normal –
- Previous diagnosis of unexplained Infertility. 3 cycles of clomiphene and 6 cycles of menopur with ovitrelle. Follicle tracking to point of mature follicle – rupture never confirmed.
- First IVF March 2011 – poor ovarian response – cancelled.
- Second IVF Aug 2011 6 follicles , 4 embryos – fragmented – 3 replaced – no success.
- AMH 2.8 nmol/l. Advised donor eggs with IVF.

Couple 3 - AMH levels 2.8pmol/l

- Repeat FSH on day 3 of cycle
- Record markers of fertility with Creighton Model FertilityCare Chart
- Supplements with vitamin D3, omega 3 and folic acid and Dietary strategy
- Naltrexone 4.5mg nocte for clinical endorphin deficiency
- Blood test on day 7 after ovulation for progesterone and oestradiol.
- Refer for repeat Laparoscopy – persistent dysmenorrhoea.



Fertility Chart

good mucus with ovulation event day 14,
 abnormal bleeding - premenstrual spotting 2-4 days.
 Low Progesterone and oestradiol day 7 after ovulation

Couple 3 - AMH levels 2.8pmol/l

- Reduced ovarian reserve - FSH 17.9 IU, LH 4.9 IU,
- Suboptimal levels of progesterone 39.6 nmol/l, oestradiol 243pmol/l
- Mild endometriosis and 1.5cm fimbrial cyst treated.

Couple 3 - AMH levels 2.8pmol/l

- Initial Treatment
 - Clomiphene 100mg daily for 3 days
 - HCG 15,000 iu – 19 mm follicle [Partial Follicle rupture](#)
- Adjusted treatment
 - Letrozole 2.5mg – 6 daily x 2 days from day 3 of cycle
 - HCG 15,000 iu – 19mm follicle
 - Cytotec 200mcg nocte for 5 days from day 11 of cycle
 - Still [Partial Follicle rupture](#)

Couple 3 - AMH levels 2.8pmol/l

- Final treatment
 - Letrozole 2.5mg – 7 tabs daily x 2 days from day 3 of cycle
 - Cytotec 200mcg nocte for 5 days from day 12 of cycle
 - Lenograstim (G-CSF) 17million iu (0.5ml) day 12 of cycle
 - HCG 15,000 iu day 13 of cycle
 - Cyclogest 400mg pv nocte x 10 nights from day 3 after ovulation
 - Naltrexone 4.5mg nocte
 - Prednisolone 2.5mg mane
- Complete follicle rupture

25/11	26/11	27/11	28/11	29/11	30/11	1/12	2/12	3/12	4/12	5/12	6/12	7/12	8/12	9/12	10/12	11/12	12/12	13/12	14/12	15/12	16/12	17/12	18/12	19/12	20/12	21/12	22/12	23/12	24/12	25/12	26/12	27/12	28/12		
H	V	V	V	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL	VL
BE																																			

Conceived on 3rd cycle of modified treatment. - Chart 3

Makinoda, S. Granulocyte Colony-Stimulating Factor (G-CSF) in the Mechanism of Human Ovulation and its Clinical Usefulness. Current Medicinal Chemistry 2008: Volume 15, Number 6, 604-613(10)

Couple 3 - AMH levels 2.8pmol/l

- Pregnancy Consultation
- Positive Foetal Heart 152 /min
- CRL = 15.5mm , 7weeks and 6 days
- **EDD 2nd Nov 2013**

Couple 3 - AMH levels 2.8pmol/l

- Treatment during Pregnancy
 - Cycogest 400mg pv twice daily – stopped at 12 weeks
 - Fematab 2mg po once daily daily – stopped at 15 weeks
 - Prednisolone 5mg mane – to stop at 24 weeks
 - Naltrexone 3mg nocte – to stop at 38 weeks
 - Supplements – Vitamin D3 – to stop at 38 weeks

Couple 3 - AMH levels 2.8pmol/l

Male or Female	Male
Birth Weight	7lb 6oz
Actual Date of Birth	12-10-2013
Estimated date of delivery	02-11-2013
Weeks of Pregnancy	37
Delivery Details	Induced ▼

RESULTS

- Three couples had successful ovulation induction and natural conception without the need for any artificial intervention.
- Each couple had full term live births and healthy babies
 - Male infant **9lbs** (4,082g) in March 2013
 - Male infant LSCS **7lb 12 oz** August 2013
 - Male infant **7lb 6 oz** induced at 37 weeks Nov 2013

Finallyconsider the alternative

- **Donor Eggs** – Irish Fertility Clinic 2007-2012
 - 104 pregnancies
 - Mean female age 40years – range 28 -49
 - Singleton 73 (70%) , Twins 22 (21%), Triplets 9 (9%)
 - **46%** had major antenatal complications
 - Hypertension 26% of pregnancies overall (45% of twins)
 - One singleton pregnancy - very severe- early onset PET – 19 weeks
had liver capsule rupture, laparotomy and hysterotomy

Finallyconsider the alternative

- Donor Eggs – Irish Fertility Clinic 2007-2012
 - **Preterm delivery** rate of 28%,
 - 11% for singletons – with one at 28 and other at 31 weeks
 - 54% (12/22) for twins – 32-36 weeks
 - 9% triplets – all delivered by c section – 5 sets very preterm
 - Over all C section rate of 77%
 - NICU – 16% singletons, 32% twins and all triplets. – **2 fetal deaths** at 19 and 32 weeks.

CONCLUSION

- For women with low AMH levels consider
 - Ovulation induction with letrozole or clomiphene
 - Ultrasound follicle tracking – with complete follicle rupture
 - Monthly blood test progesterone and oestradiol - day 7 after ovulation
 - Standardised Fertility Chart

ANY QUESTIONS?

For more Information see here

www.naprofertility.ie