Low AMH and natural conception

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Galway, Ireland

IIRRM Annual Meeting, 7th August 2013

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 cannot 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

- **Granulosa cells of ovary**
- **Indicate size of antral follicle pool**

- **Predict ovarian response to stimulation**
- **Tailor treatment to individual**

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

There are 2 different assays used by labs

1) **Immunotech- Beckman (Higher Readings)**
2) **DSL (5-7 times lower)**

Follow reference ranges of lab

Note a 3rd standardised test is in development

Anti Mullerian Hormone

AMH Assay

Furthermore results can be reported in pmol/l or ng/ml

The conversion factor is 1 pmol/l = 7.14 ng/ml

Therefore if AMH is 1 it could be as high as

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

….and converted from DSL to Beckman (x5) = 35.7 ng/ml

So check the reference range for your lab before interpreting a result!

Anti Mullerian Hormone

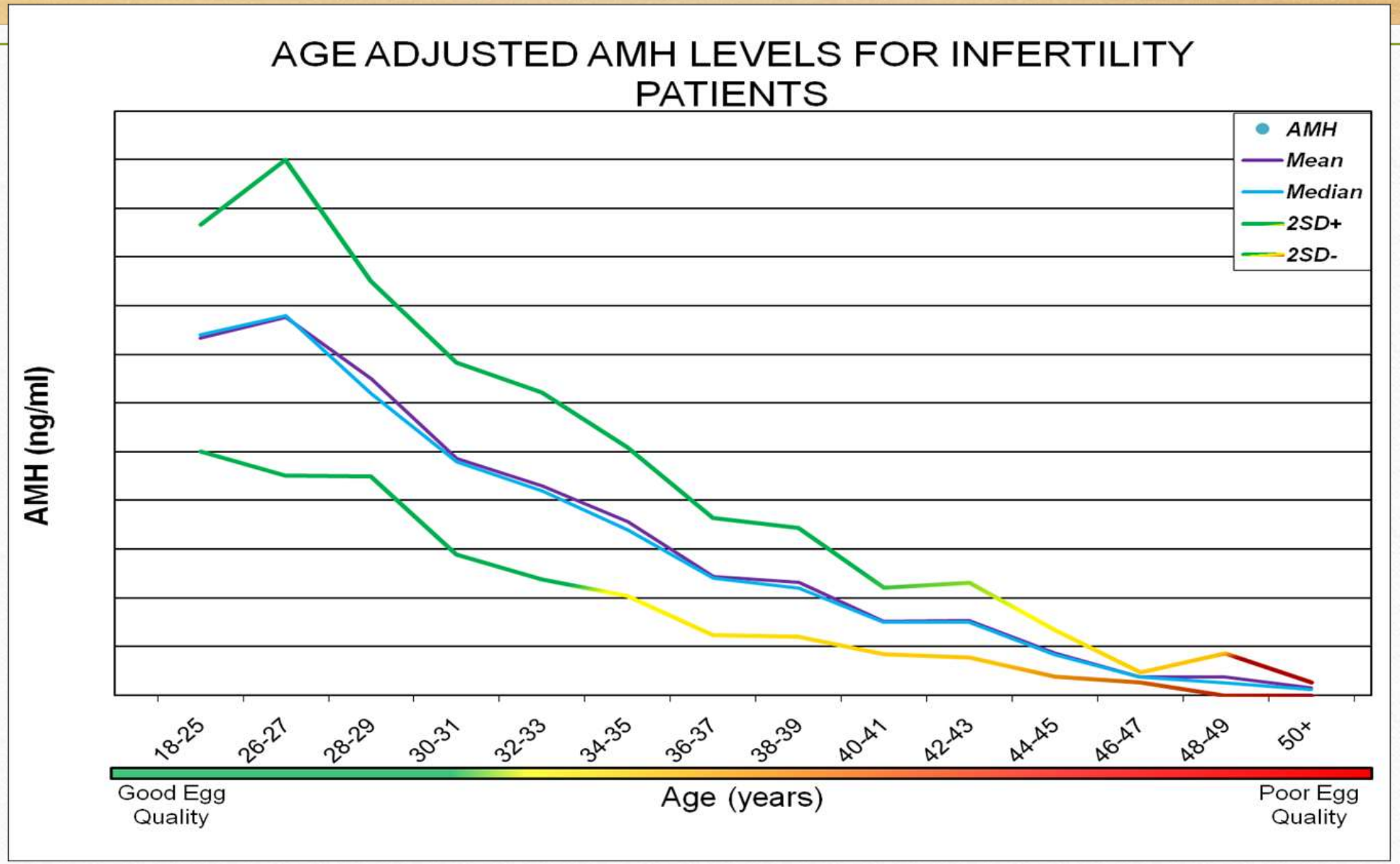
- **Low levels**
  - **Low antral follicle pool**
  - **Reduced ovarian reserve**
- **High Levels**
  - **PCOD**

Anti Mullerian Hormone

- **Reduced Ovarian Reserve**
  - **Age**
  - **Blood**
    - **FSH >10 iu, Oestradiol, Inhibin B, AMH**
  - **Ultrasound**
    - **Ovarian Volume<3cm^2, 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**



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 (0.5ng/ml)
- Couple 2 - AMH levels 3.2pmol/l (22.8ng/ml)
- Couple 3 - AMH levels 2.8pmol/l (19.9ng/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.

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

Treatment Plan

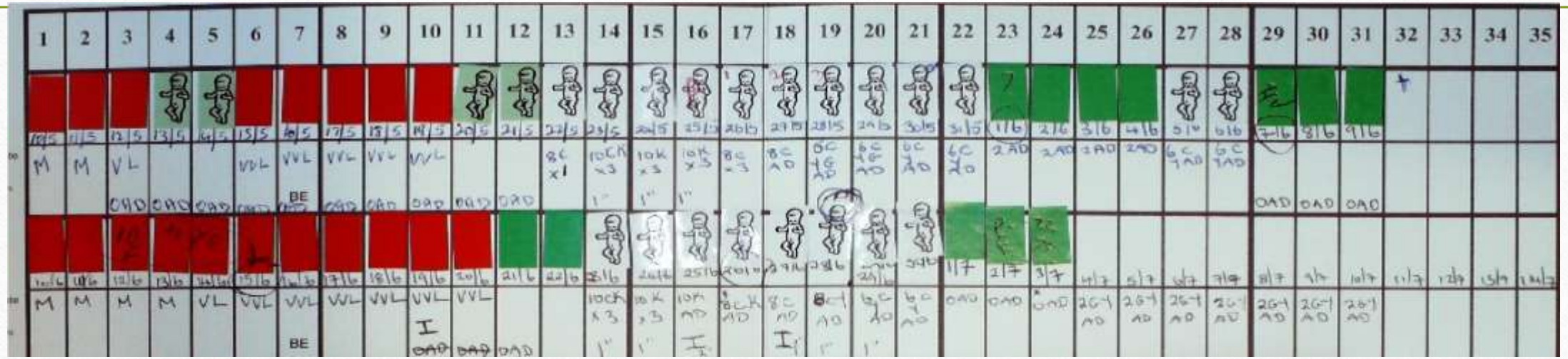
Letrozole 2.5mg – 10 tabs day 3
HCG 10,000 iu mid cycle
prednisolone 5mg mane
naltrexone 3mg nocte

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



- Positive Foetal Heart
- CRL = 14.8mm , 7weeks and 6 days
- EDD 22nd March 2013

Couple 1 - AMH levels 0.07pmol/l

- Treatment during Pregnancy
  - Cycogest 400mg pv twice daily
  - Fematab 2mg bd po twice daily
  - Naltrexone 3mg nocte
  - Prednisolone 5mg mane
  - Supplements – Vitamin D3 and Folic Acid

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

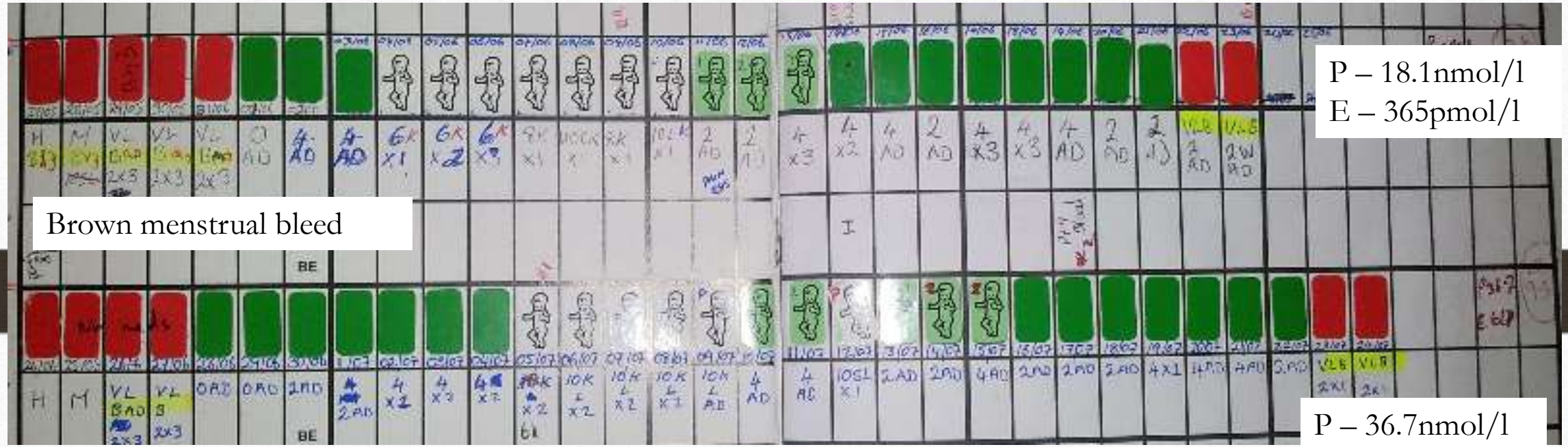
- Presented in May 2012
- History Gravida 1 Para 0. Female 35 years. Male 36 years.
- Intercourse without contraception for 5 years, since June 2007.
- Laparoscopy – Mild endometriosis 2009. Hysteroscopy normal Nov 2011.
- Semen analysis normal. Day 3 bloods and clotting studies normal. AMH 3.2 pmol/l.
- 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

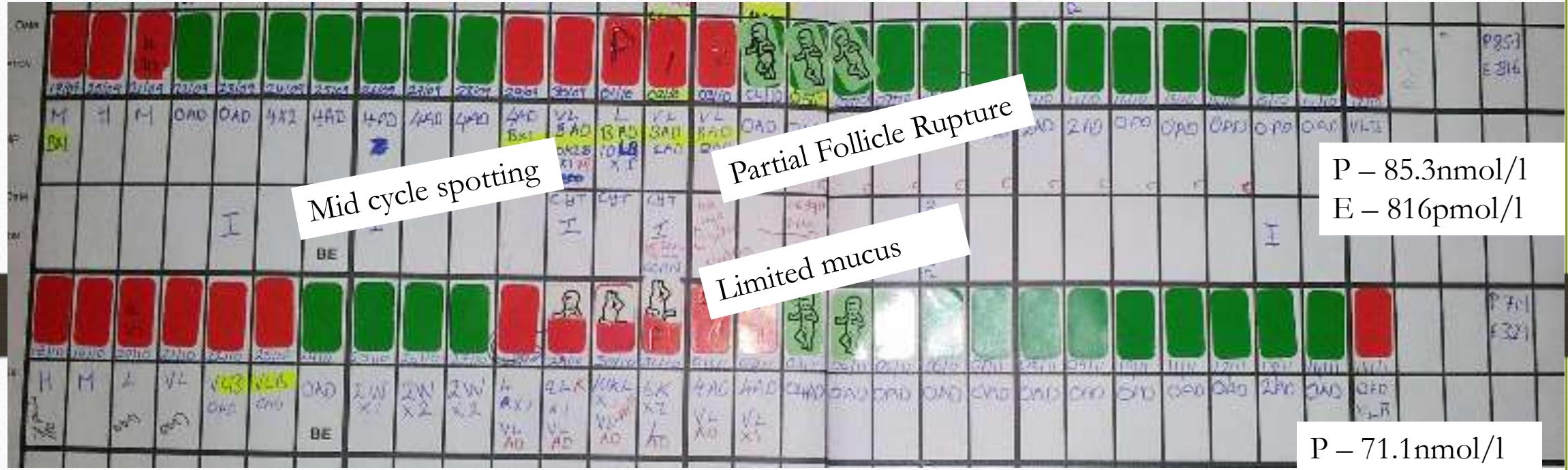

Brown menstrual bleed
P – 18.1nmol/l
E – 365pmol/l
P – 36.7nmol/l
E – 627pmol/l

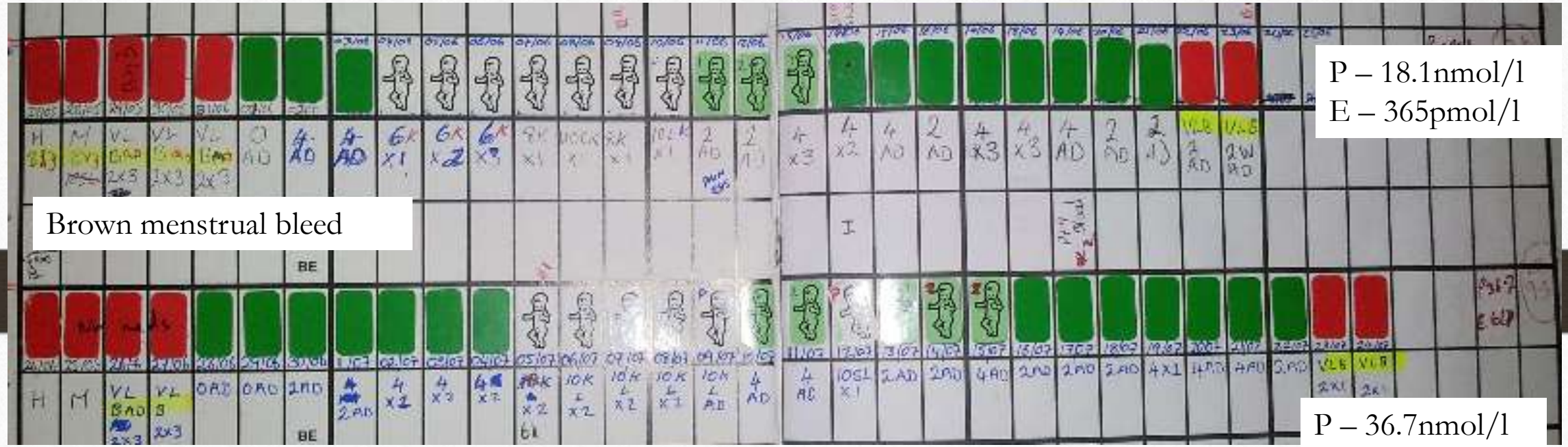
Couple 2 - AMH levels 3.2pmol/l

- 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

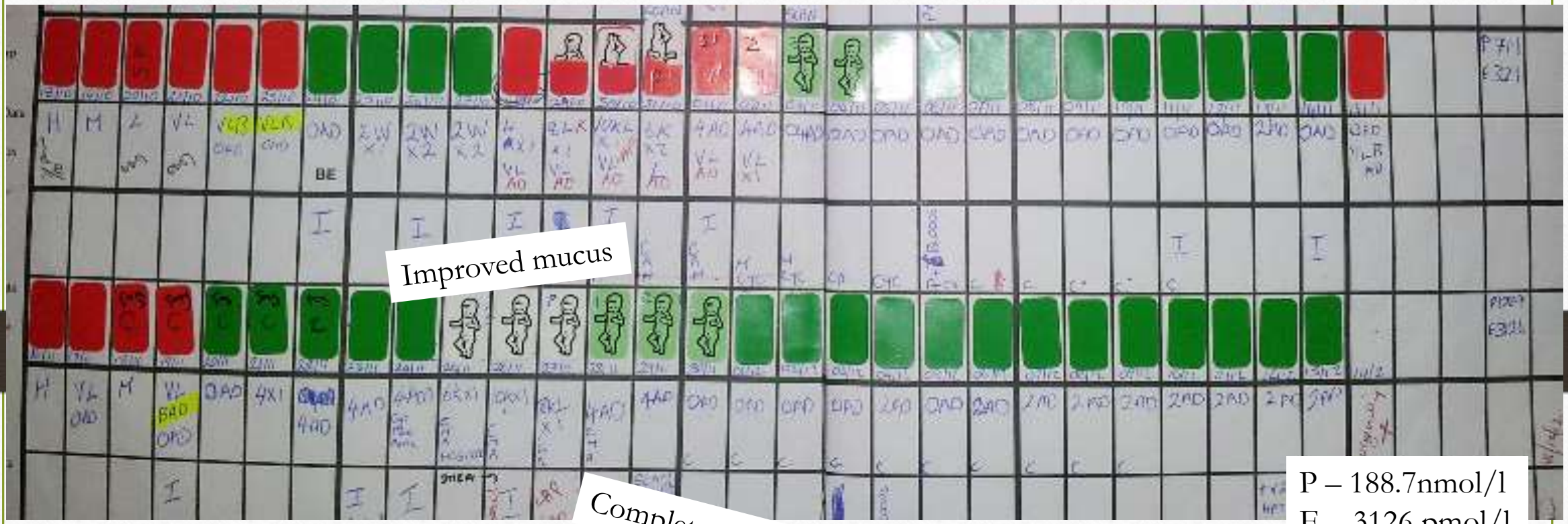
- Results
- Fertility Chart
  - Limited cervical mucus flow
  - Mid cycle spotting
- Ultrasound Follicle Tracking
  - Partial –incomplete rupture

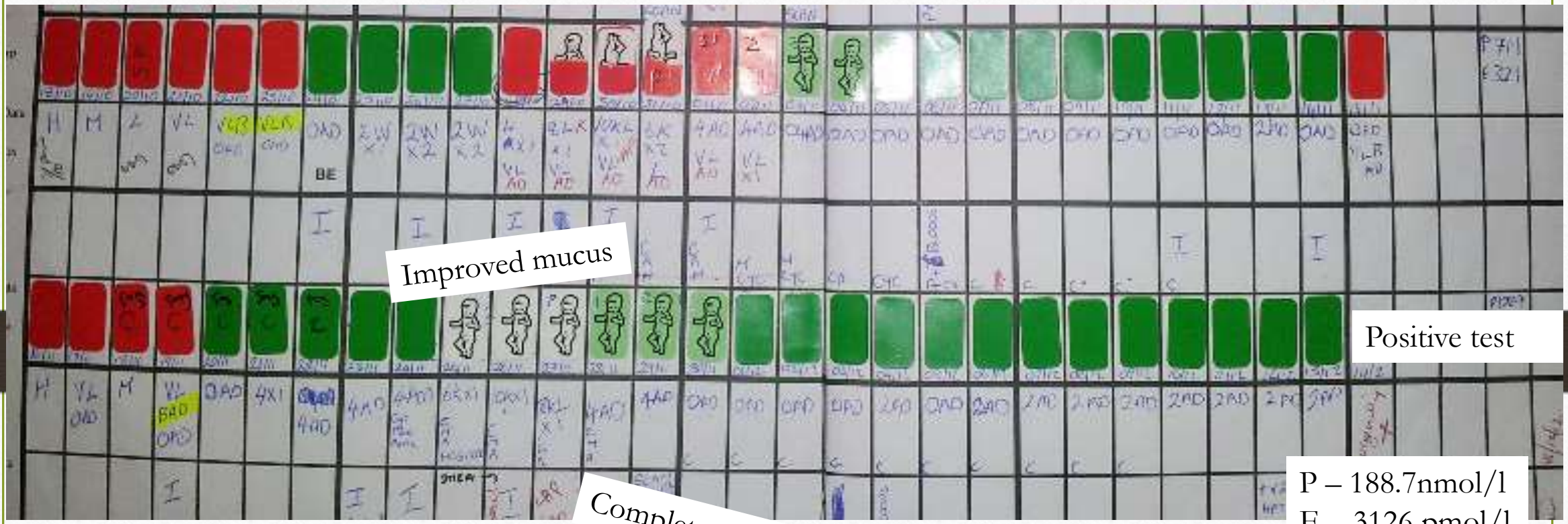

Mid cycle spotting
Partial Follicle Rupture
Limited mucus
P – 85.3nmol/l
E – 816pmol/l
P – 71.1nmol/l
E – 329pmol/l


Brown menstrual bleed
P – 18.1nmol/l
E – 365pmol/l
P – 36.7nmol/l
E – 627pmol/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

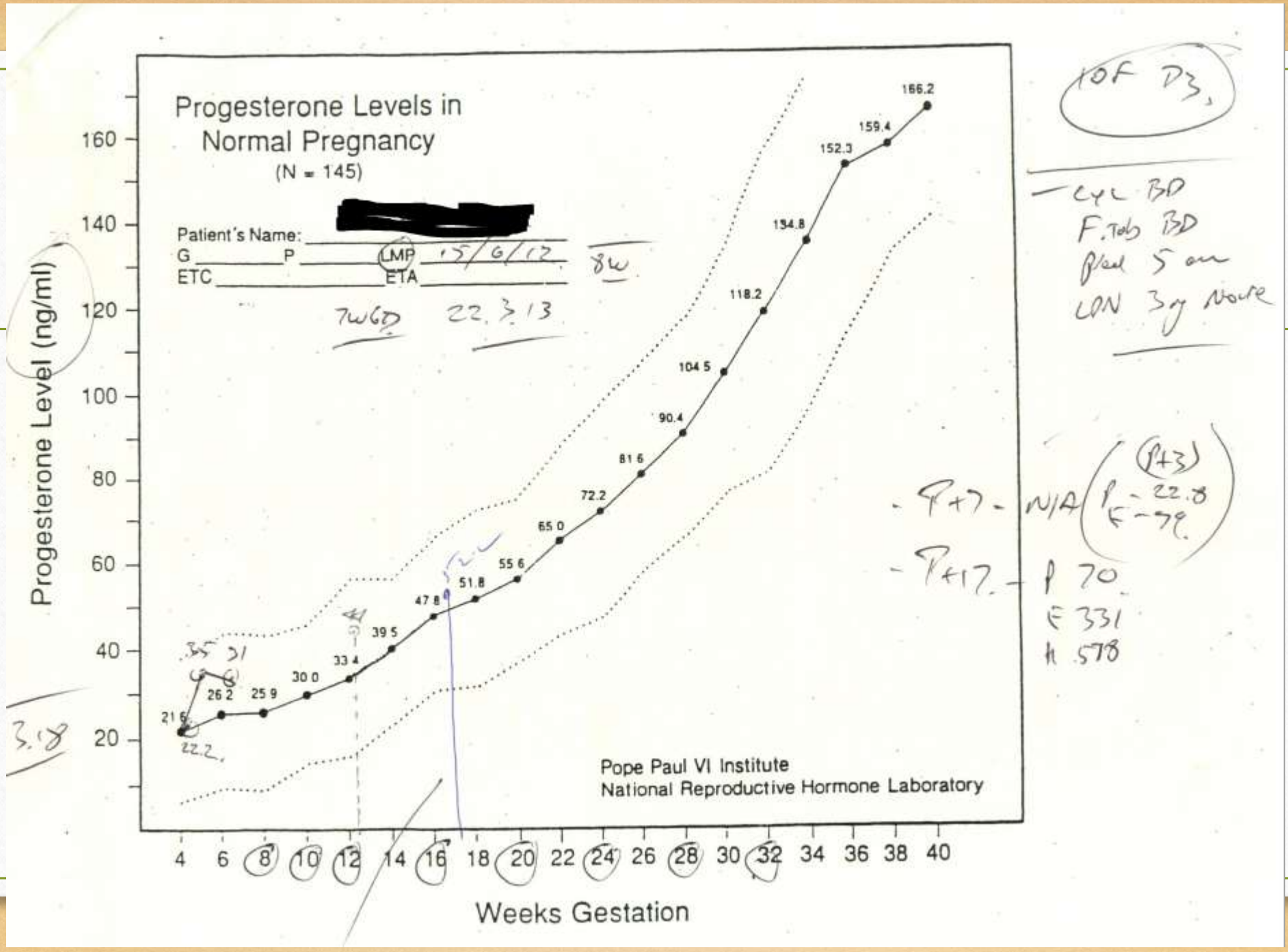
Couple 2 - AMH levels 3.2pmol/l

- 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
- Pregnancy ongoing as of 15th July– 34 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

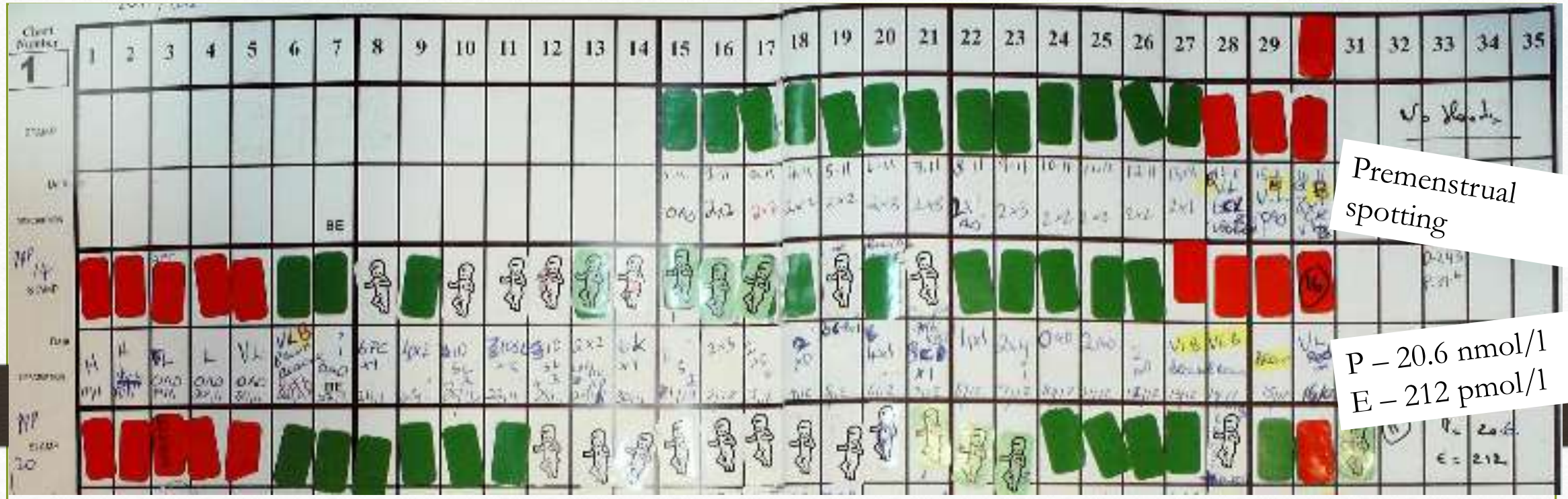

Progesterone Levels in
Normal Pregnancy
(N = 145)
Patient's Name: [redacted]
G ____ P ____ LMP 15/6/12
ETC ____ ETA ____
7w6D 22/3/13
8w
Progesterone Level (ng/ml)
160
140
120
100
80
60
40
20
21.6
22.2
26.2
25.9
30.0
33.4
39.5
47.8
51.8
55.6
65.0
72.2
81.6
90.4
104.5
118.2
134.8
152.3
159.4
166.2
Pope Paul VI Institute
National Reproductive Hormone Laboratory
4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Weeks Gestation

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

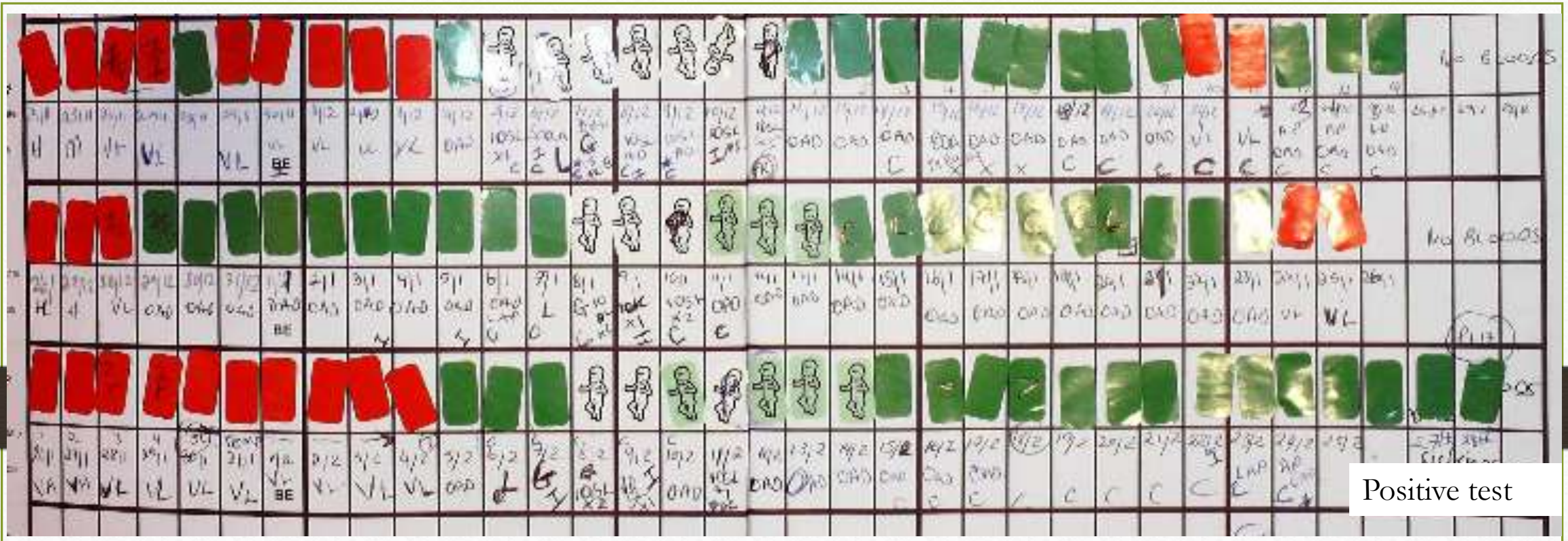
- Reduced ovarian reserve - FSH 17.9 IU, LH 4.9 IU,
- Suboptimal levels of progesterone 39.6 nmol/l, oestradiol 243pmol/l
- Mild endometriosis and 1.5cm fimbrial cyst treated.

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



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
- Pregnancy ongoing as of 9th May 2013 – 15 weeks

RESULTS

- Three couples had successful ovulation induction and natural conception without the need for any artificial intervention.
- One couple had a full term live birth of a male infant weighing 9lbs (4,082g) in March 2013. The remaining couples are due to deliver in August and November 2013 respectively.

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

Finally …..consider 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

Finally …..consider 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.

Premature Ovarian Failure

- 2 Case Reports

1. FSH 23iu
2. AMH 0.07pmol/l

Premature Ovarian failure

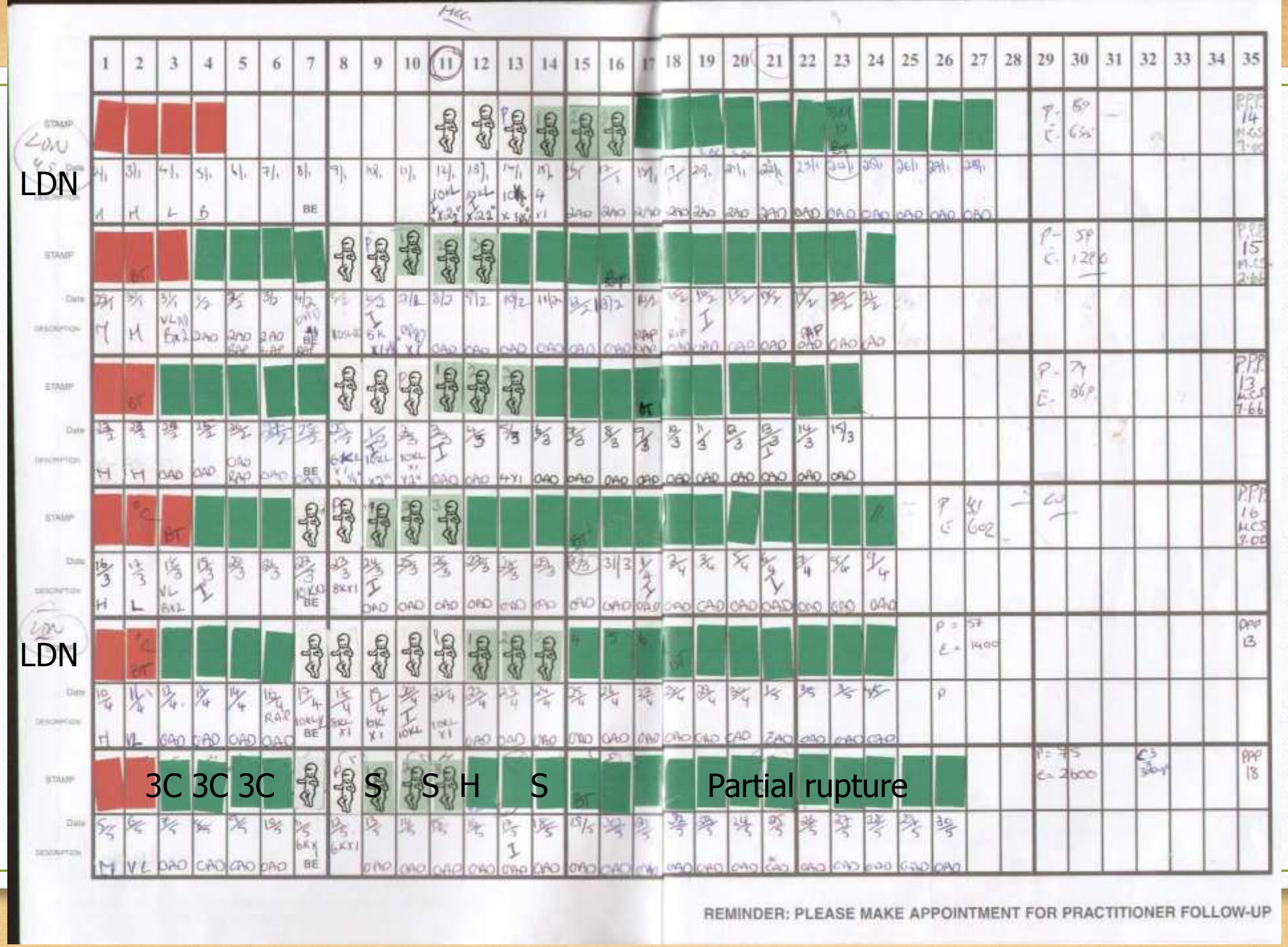
- April 2008, 35yo G0 P0
- 18-30 day cycle
- DX Premature Ovarian failure
  - Raised FSH **23.7iu**

Premature Ovarian failure

- Previous Treatment
  - Clomiphene x5 cycles
  - IUI x 4 cycles
  - IVF
    - Sept 2006 – 1 Follicle – cancelled
    - Oct 2007 – Flare Protocol – No follicles

Premature Ovarian failure

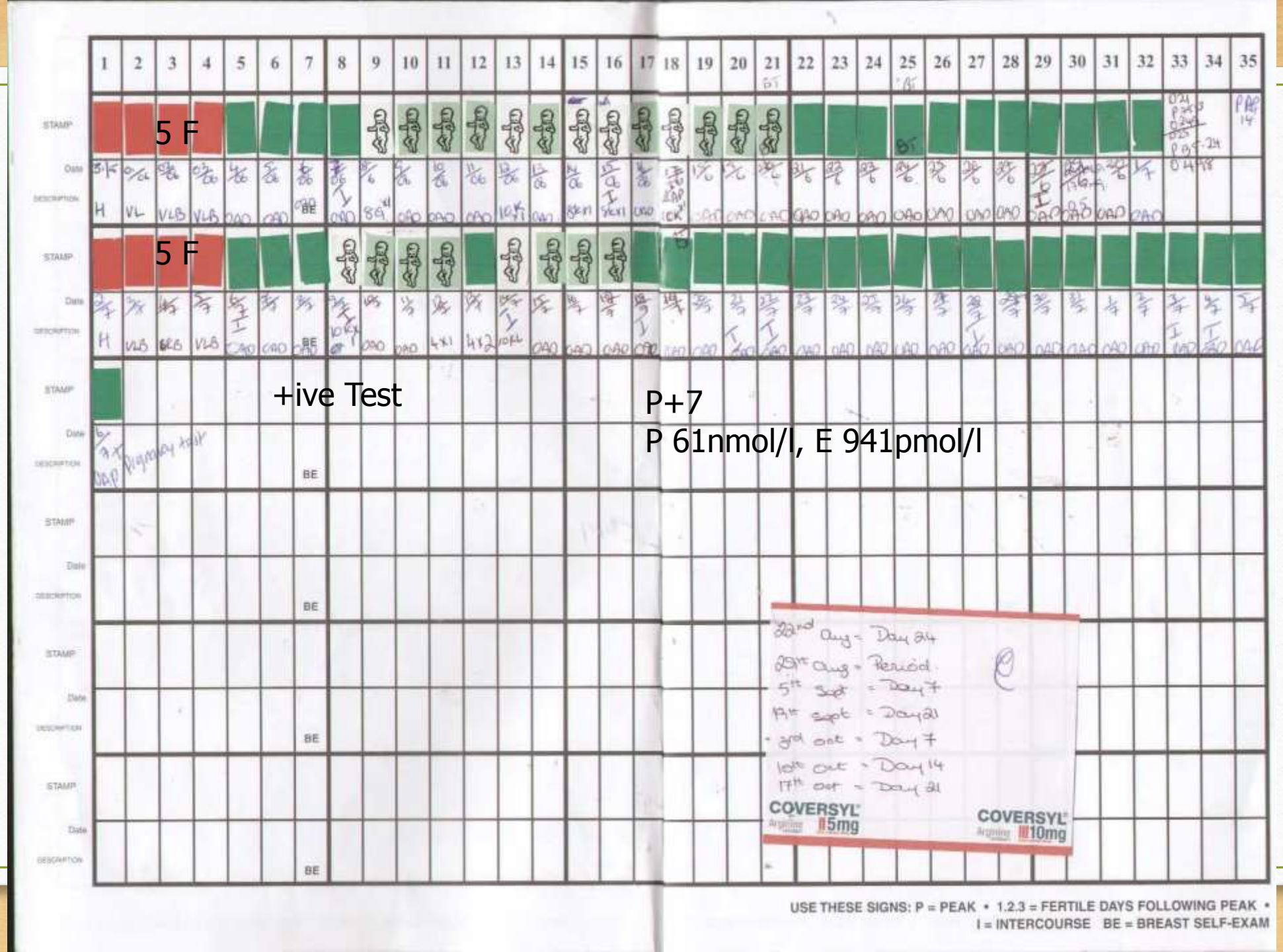
- NPT Plan
  - FoodPrint
  - D3 2,400iu, Ca, Mag, Probiotics, Omega 3
  - LDN 4.5mg
  - Ovulation induction – clomiphene
  - Bolus HCG 10,000iu

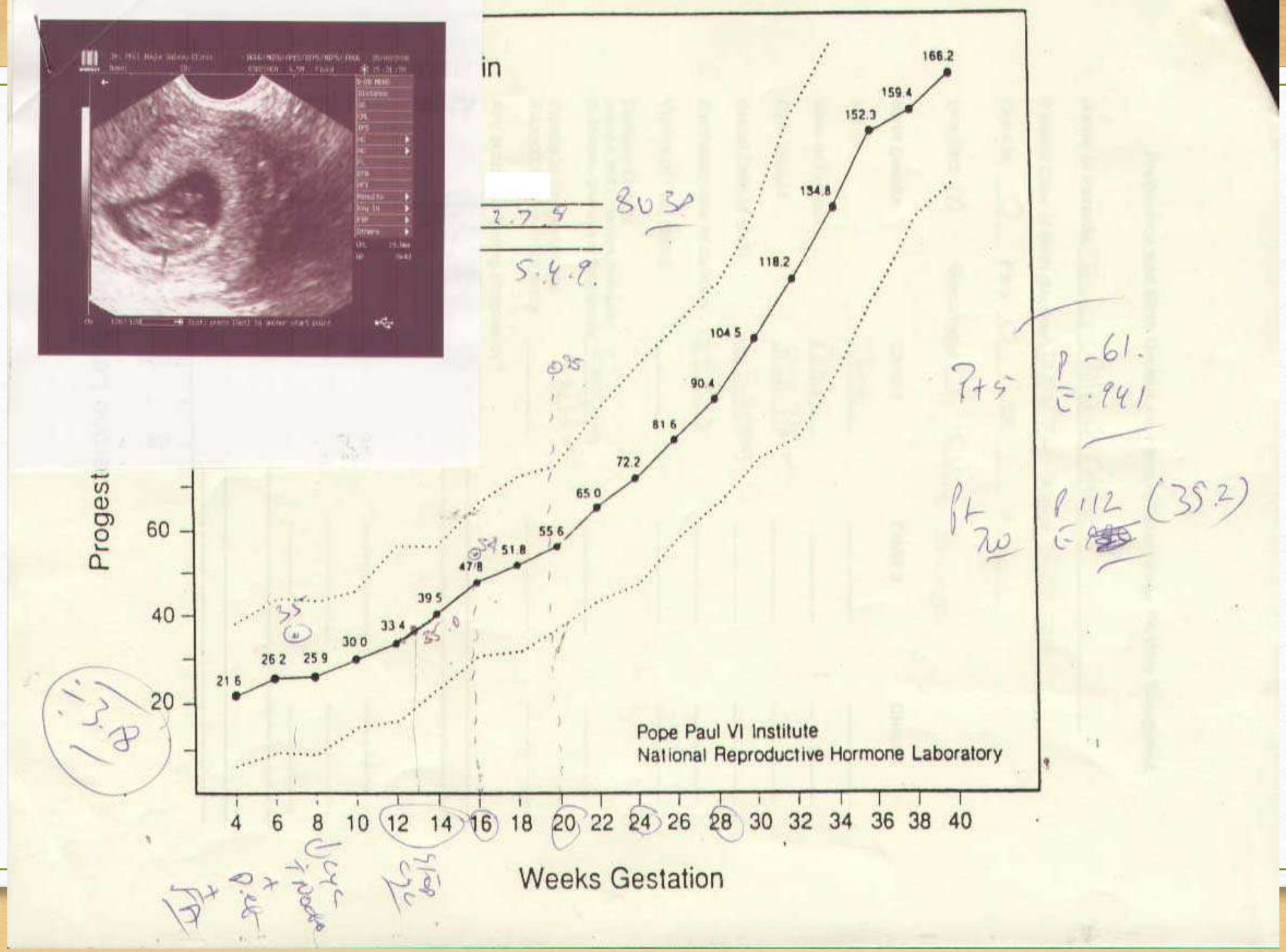

LDN
LDN
3C 3C 3C S S H S
Partial rupture
REMINDER: PLEASE MAKE APPOINTMENT FOR PRACTITIONER FOLLOW-UP

Patient Number: 7414
Test Date: 13-May-08

Fax 44 (0) 1353 863330
www.cambridge-nutritional.com
labtests@cambridge-nutritional.com

Type	Avoid (>60)	Borderline (40-60)	No reaction
dairy	COW'S MILK (448)	EGG WHITE	
dairy			
dairy	EGG YOLK (121)		
dairy	GOAT MILK (64)		
fish/seafood			COD
fish/seafood	CRAB (75)		HADDOCK
fish/seafood			
fish/seafood	LOBSTER (109)		
fish/seafood	OYSTER (92)		PLAICE
fish/seafood			SALMON
fish/seafood		SHRIMP/PRAWN	
fish/seafood			TROUT
fish/seafood			TUNA
fish/seafood			
fruit			APPLE
fruit			AVOCADO
fruit			BLACKBERRY
fruit			CHERRY
fruit			GRAPE
fruit			GRAPEFRUIT
fruit			LEMON
fruit			LIME
fruit			ORANGE
fruit			PEAR
fruit		PINEAPPLE	
fruit			RASPBERRY
fruit			STRAWBERRY
fruit			
grain			BARLEY
grain	CORN (maize) (61)		
grain			DURUM WHEAT
grain			GLIADIN
grain			OAT
grain			RICE
grain			RYE FLOUR
grain			WHEAT
grain			
herb/spices			GARLIC
herb/spices			GINGER
herb/spices			MUSTARD SEED
herb/spices		PEPPERCORNS (B/W)	
herb/spices			RED CHILLI
meat			BEEF
meat			CHICKEN
meat			LAMB
meat			PORK
meat			TURKEY
nut	ALMOND (64)		BRAZIL NUT
nut			CASHEW NUT
nut			HAZELNUT
nut			PEANUT
nut			
nut	PISTACHIO (77)		
vegetable		BEAN (red kidney)	
vegetable			BEAN (white haricot)
vegetable			BROCCOLI
vegetable			BRUSSEL SPROUT
vegetable			CABBAGE
vegetable			CARROT


5 F
5 F
+ive Test
P+7
P 61nmol/l, E 941pmol/l
22nd Aug = Day 14
29th Aug = Period
5th Sept = Day 7
12th Sept = Day 21
3rd Oct = Day 7
10th Oct = Day 14
17th Oct = Day 21
COVERSYL 5mg
COVERSYL 10mg
USE THESE SIGNS: P = PEAK • 1.2.3 = FERTILE DAYS FOLLOWING PEAK •
I = INTERCOURSE BE = BREAST SELF-EXAM



Progest
60
40
20
21.6
26.2
25.9
30.0
33.4
39.5
47.8
51.8
55.6
65.0
72.2
81.6
90.4
104.5
118.2
134.8
152.3
159.4
166.2
4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Weeks Gestation
Pope Paul VI Institute
National Reproductive Hormone Laboratory

Pregnancy and Birth Details after NaproTechnology Fertility Treatment

Name of Parents [redacted]

Parents Date of Birth (Mother) 21.08.72 Father 13.08.74

Gravida 0 Para 0 SA ____ IA ____

Live Birth ☑ Miscarriage ☐ Trying 5 yrs.

Birth Details	**Child 1**	C
Name	____	
Male or Female	Male	
Birth Weight	8LB 7½ oz.	
Actual Date of Birth	26.3.2009	
Estimated date of delivery	5.4.09	
Weeks of Pregnancy	____	
Delivery Details Induced, NVD, Forceps, Vacuum C-Section – Planned or Emergency	Emergency Section	
Weeks of Progesterone Support during Pregnancy	____	

Any problems during Pregnancy?

Any problems with baby?
e.g. Intensive Care after delivery (Days) ____

Heart or breathing problems? ____

Ongoing health problems? ____

Comments:

Premature Ovarian Failure

- Recent Case

Premature Ovarian Failure

G0P0

- **Age 36 years**
- **FSH 45iu**
- **AMH…….**

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.