

Pathology news

April 2014 – Referral Labs Edition

Patient Focussed and User Friendly Referral Services

Welcome to our annual Pathology News for referral laboratories.

Each April we provide you with information about our services, including key changes that are being made, up to date turn round data, and also our latest price list. In this edition we have aimed to give our users some audit detail which we hope you will find useful and may consider using locally.

We have a special feature on our Clinical Toxicology Laboratory where new exciting services that we have been developing for the last three years are now in use. Also, we are keen to look at further implementation of electronic result return and have several new approaches that we are going to be working on in coming months with our users.



Sample Reception at Sandwell

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Referral Laboratories and Service Level Agreements

As a major referral laboratory to NHS Trusts around the United Kingdom we understand the pressure people are now under to have Service Level Agreements. To help in this we are designing a new Service Level Agreement which we will be offering to all our current users in the next few months. In this way we do hope that the bureaucracy of complying with new UKAS accreditation processes will be helped.

See us at...

EuroLabFocus

The 3rd EFLM-UEMS Congress

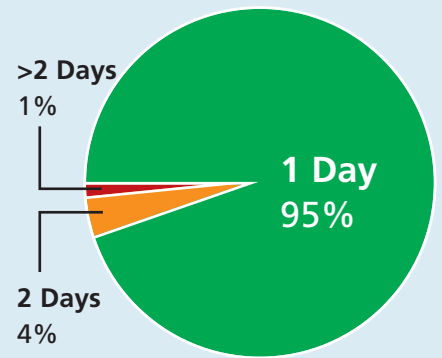
We look forward to meeting many of our referral laboratory users at the EuroLabFocus meeting in Liverpool, 7-10 October 2014.

TPMT Service Yearly Statistics

Our stated turn round time is 1 day for TPMT activity, unless further DNA confirmation is required. An audit over the past year showed the average monthly turn round for TPMT was 1 day.

For 99% of all TPMT requests, results are available within the target as shown. Results exceeding target were generally waiting for genotype or repeat results.

Breakdown of current turn round times for TPMTs received



	Total TPMT Requests	Deficient (<10 mU/L)	Low (20 - 67 mU/L)	Normal (68-150 mU/L)	High (>150 mU/L)
Number	34,642	110	4,305	29,714	513
% of total	100	0.3	12.4	85.8	1.5

TPMT status for patient samples received for 12 months (March 2013 – February 2014)

Genotype Studies

An audit of TPMT genotypes for each of the identified deficient patients showed 88% were homozygote for the TPMT*3 mutation (3*/3* genotype) and 5.5% were found to be compound heterozygote for the TPMT*2 / TPMT*3 mutations (2*/3* genotype). These two genotypes confirm deficient TPMT activity.

Just 0.9% patients were found to be heterozygote for the TPMT*2 mutation (1*/2* mutation) and 5.5% (6 patients) were found to be



heterozygote for the TPMT*3 mutation (1*/3* mutation). In these latter two categories, the deficient TPMT activity is likely to be attributed to the presence of another rare mutation, since samples are screened for the

common mutations: TPMT*3A/*3C and TPMT*2 only, which account for 60-95 % of all mutant alleles for deficient TPMT activity. This clearly demonstrates the benefit of phenotyping as the first line screening approach.

	Total Genotype Confirmations	3*/3*	2*/3*	1*/3*	1*/2*
Number	110	97	6	6	1
% of total	100	88.2	5.5	5.5	0.9

Key Information for TPMT Service Users

- **Sample storage:** Samples should be stored at 4°C prior to dispatch. Please ensure samples are not frozen.
- **Sample stability:** TPMT activity is stable for 6 days at room temperature and for at least 12 days at 4°C. We highlight samples >8 days old on receipt.
- **Blood transfusion:** Samples from patients who have received recent blood transfusions (within 90 days) can give misleading results.

Therefore, please provide details of recent transfusions on the request form so we are able to perform TPMT genotyping for confirmation of the patient's TPMT status.

- **TPMT genotyping:** DNA studies are offered as a confirmatory service to confirm TPMT status in selected patients, but not offered as a primary test. Criteria for performing TPMT genotyping:

- Confirmation of deficient TPMT status
- Change in TPMT status
- Low haematocrit and low TPMT activity to check for falsely low TPMT activity
- Recent blood transfusion
- Previous severe reaction to thiopurine drugs
- Pancytopenia, neutropenia or myelosuppression.



Stone Analysis

The renal stone service has been available for over 20 years at SWBH NHS Trust. In the last five years, due to increasing demand, we have expanded the range of urine markers used to screen patients with renal stone disease.

Our standard stone screen includes urine oxalate, citrate, calcium, phosphate, urate and magnesium. We have audited data produced from our laboratory over the past two years and have found interesting relationships between co-morbidities and the prevalence

of renal stone disease. Our data shows there are strong links between common and emerging diseases such as diabetes and obesity that may increase the risk of patients developing renal stones.

We have a fast and efficient urine screening service with a turn round time of five days for a complete stone screen. Automation of our citrate and oxalate methods now provides a more efficient service. Urine oxalate and citrates are performed weekly and can be requested singularly or together.

Our new FTIR laboratory



Trace Elements

Over the past 12 months our Trace Elements service has moved to a purpose built laboratory that hosts three ICP-MS analysers at our Sandwell site.

The laboratory has been designed to provide the highest level of quality and to eliminate sample contamination. Our three analysers are used to provide an efficient service for trace metals, toxic metal screens and a number of other services.

In particular:

- We have a dedicated service for Chromium and Cobalt monitoring in metal on metal (MoM) hip joints with a 2 day turn round and clinical advice.
- Our laboratory participates in specialist EQA schemes to cover a wide range of analytes in various samples matrices.
- Due to increasing demand we have now developed a routine method to distinguish between dietary and non-dietary Arsenic.

The service is now headed by Dr Nicola Barlow,
Tel: 0121 507 3517, Email: nicola.barlow1@nhs.net

Infliximab Monitoring & Biological Drug Testing

We have developed and implemented a routine monitoring service for Infliximab and antibodies.

There has been increasing interest from users of the service as it proves to be a vital step towards personalising infliximab therapy. Our data shows good correlation between drug levels and markers of inflammation.

We have data from a Gastroenterology patient cohort showing a good relationship between drug levels and faecal calprotectin. Data from our Rheumatology patient cohort shows a similar relationship exists between CRP and drug levels.

Current turn round time is 5 days for Infliximab levels and 7 days for antibody levels. Prices are £25 for drug levels and £35 for antibody levels.



Our New Clinical Toxicology Service

Over the last three years our Toxicology Laboratory R&D focus has been to create a relevant service suitable for the modern clinical situations presented to us.

We have invested over £1 million in new equipment and have a new team of scientific staff excitingly taking our services forward. Our state of the art techniques are now available routinely to other laboratories with key developments being:

- Moving away from immunoassay
- Simplifying our approach
- Providing clinically robust information, and overall cost reduction for users
- Ability to detect the many new drugs of abuse being used in the UK
- New techniques for our 'unknown drug screen' service.

Drivers for Change

Historically there have been major disadvantages to using immunoassay for drugs of abuse screening including:

- Poor sensitivity with false negatives
- Lack of specificity with false positives
- Identifying drug classes rather than individual drugs, for example: reporting 'opiates' rather than codeine, morphine, dihydrocodeine, 6-monacetylmorphine (heroin use specific marker) separately can be very misleading. Clinicians trying to interpret such results can experience patient-doctor disputes.

Immunoassay testing best practice is to confirm positive screen results with sensitive and specific methods such as Capillary GC or LC-MS/MS.

However, this delays turn round of results and has a high cost so in practice many laboratories try to 'get away' without any confirmation. Previously we charged an additional £26 on top of the cost of the initial immunoassay screens for every confirmation we performed. Now, by our new techniques the total price for the 'Screen and Confirmation' is just £20.

Goodbye Immunoassay!

Our routine LC-MS/MS oral fluid drug screening service commenced in September 2012. This service has given us considerable experience of LC-MS/MS as a first line approach. In January 2014 we switched our high throughput urine drug screening service from immunoassay to LC-MS/MS. Both urine and oral fluid services now look for the same 26 drugs and metabolites, with this repertoire trying to reflect the most common substances misused in the UK population. The flexibility to alter the repertoire as fashions in substance misuse change is of course fundamental to this service.

Right Result First Time

Our new drugs of abuse services use LC-MS/MS on every sample. Positive cut-off thresholds are much lower

than immunological methods and we detect and report individual drugs rather than drug class.

- Multiple reaction monitoring (MRM) for every drug
- Monitoring 2 MRM (Quantifier and Qualifier) reactions
- Calculation of drug specific target Quantifier/Qualifier ratios
- Drug specific retention times
- Inclusion of deuterated standards to correct for ion suppression or enhancement

Our new service eliminates the need for separate screen and confirmation, making testing much cheaper. We use the same method for every sample and even if you just request confirmation of a cocaine positive result we still report all 26 drug results to you. You need to understand that often we uncover poor quality results by immunoassay when we analyse samples that have been previously screened locally. Our target turnaround is <48 working hours on receipt and for urgent samples <3 hours.

Street Highs

An increasing problem has been the rise of 'street high' use in the UK.



Dr Loretta Ford, who heads up our Toxicology Laboratory assisted by Meenal Chauhan on the LC-QTOF analyser



Andy Whiles, Wendy Tidbury and Rachel Jones using a LC-MS/MS analyser

These designer drugs, which mimic the effects of classic drugs of abuse, are readily available in 'head shops' and on the internet. They are not detected by most immunological techniques and there is growing concern about the lack of specific testing in the UK.

We are the first NHS laboratory to routinely screen for street highs such as mephedrone (meow, meow, MCAT) on every sample you send to us.

Cannabis

Currently we still analyse cannabis separately by immunoassay and the cost of a cannabis screen is just £7. We are working on a new LC-MS/MS method which will include the new synthetic cannabinoids that are now being sold and used throughout the UK.

New LC-QTOF Service

For unknown toxicology screening we now use LC-QTOF (time of flight) as our primary technique. This 'exact mass' analyser measures to 3 decimal places (<1 mDa). Our LC-QTOF drug library has been created using exact mass of the compound (precursor), the fragment ion data and the specific drug retention time, giving great specificity. We look for over 1,200 drugs and metabolites and are constantly adding to this repertoire as new drugs are found in patient samples.

We can analyse liquids, powders and pills by LC-QTOF which lends it to multiple clinical questions. Now we have two approaches to 'unknown drug' screens:

- **LC-QTOF screen: A one off analysis for any sample, costing £80**
- **Full unknown toxicology screen at £300**

LC-QTOF Screen

Interestingly, our users are creating their own clinical services using our LC-QTOF service – examples include:

Checking Drug Compliance:

Investigation of resistant hypertension by screening for multiple drugs. There are over 50 antihypertensive drugs in the LC-QTOF library.

'Street High' Investigation: Street high use is both fashionable and fast moving, with new drugs emerging all the time. One of the challenges with street highs is to identify not only parent drugs but more importantly metabolites. Often

commercial products contain a number of different active chemicals. Our LC-QTOF library includes over 60 new legal highs and is growing by the week.

Unusual Requests: LC-QTOF is also useful for testing those strange requests laboratories receive now and again, and don't know what to do with. Some recent examples are shown in the Q&A box below.

Full Unknown Toxicology Screen

Unknown toxicology screens represent a lot of work on our specialist equipment. This service comprises:

- **LC-MS/MS drug screen**
- **Cannabis; alcohol; barbiturates and LC-QTOF screen**

Results can be diagnostic, for example identifying antipsychotic drug use in a safe-guarding child case, where the patient had multiple previous hospital admissions without detecting the underlying problem.

We have the option to quantitate certain drugs in individual cases. Our goal is to report preliminary results the same working day. We work closely with duty biochemists and clinicians during an investigation as often further clinical details are needed as the laboratory studies proceed.

Q: "My patient has stopped using Azathioprine after buying 'miracle cream' off the internet."

A: LC-QTOF showed the cream contained the potent topical steroid clobetasol propionate.

Q: "My patient is using an Indian herbal remedy for relief of asthmatic symptoms and now has a cortisol of <15nmol/L."

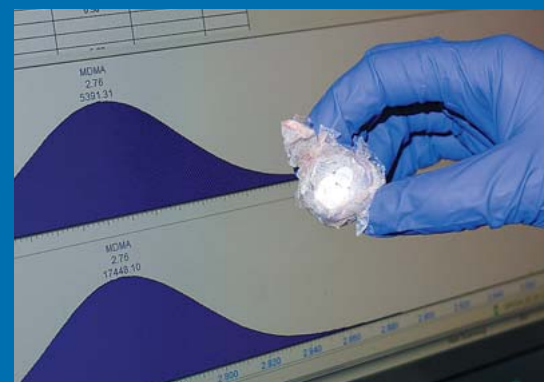
A: LC-QTOF showed the remedy to contain dexamethasone

Q: "We have found these tablets when searching the room of a patient on a secure ward and suspect he may be dealing. If so we will prosecute!"

A: LC-QTOF identified these homemade tablets to consist of the sweetener aspartame!

Q: "We have removed this ball of white tablets wrapped up in clingfilm (see photo below) from the throat of a patient – what does it comprise of?"

A: The active ingredient of the white tablets was determined as MDMA (3,4-methylenedioxy-N-methylamphetamine or Ecstasy)



Specialist Assays

Prices and turn round targets* offered to NHS Contracts

*Where days are given these are working days.

Biochemistry	Turn round	Cost
ACE	3 days	£15
Bile Acids	1 day	£15
Caeruloplasmin	2 days	£15
Carotenes	5 days	£35
Faecal Calprotectin	3 days	£25
Faecal Elastase	3 days	£33
Fructosamine	1 day	£15
Gilberts Syndrome	3 days	£30
Pro Collagen Type 3 Peptide (P3NP)	7 days	£20
Cholinesterase	within 24 hours	£15
RBC Cholinesterase	within 24 hours	£50
Pharmacogenomics	Turn round	Cost
Thioguanine Nucleotides	2 days	£27
TPMT Service	1 day	£20
Serum Infliximab	5 days	£25
Anti Infliximab Antibodies	7 days	£35
Fat soluble vitamins	Turn round	Cost
25-hydroxyvitamin D ₂ & D ₃ Serum/Plasma	2-3 days	£10
Vitamin A	2-3 days	£13
Vitamin E	2-3 days	£13
Blood spot analysis	Turn round	Cost
25-hydroxyvitamin D ₂ & D ₃	2-3 days	£16
Stone service	Turn round	Cost
Stone Analysis	5 days	£28
Urine Citrate	5 days	£15
Urine Oxalate	5 days	£15
Urine Stone Screen (calcium, phosphate, citrate, oxalate, magnesium, urate)	5 days	£50
Trace Elements	Turn round	Cost
Aluminium	2-5 days	£25
Arsenic	2-5 days	£25
Cadmium	2-5 days	£25
Chromium	1-2 days	£20
Cobalt	1-2 days	£20
Chromium & Cobalt	1-2 days	£30

Trace Elements continued	Turn round	Cost
Copper (unine)	2-3 days	£20
Lead	2-3 days	£20
Lead HB ZPP	2-3 days	£35
Manganese	2-3 days	£20
Mercury	2-5 days	£25
Nickel	2-5 days	£25
Selenium, Copper & Zinc	1-2 days	£15ea
Toxic Metals Screen	1-2 days	£100
Gold	2-3 days	£40
Bromide	2-3 days	£40
Other Metals	2-5 days	£40
Therapeutic drugs	Turn round	Cost
Caffeine	1-2 days	£20
Clozapine & Norclozapine	2-3 days	£20
Lamotrigine	2-3 days	£20
Lithium	1 day	£10
Olanzapine	3 days	£30
Levetiracetam	4 days	£30
Melphalan	4 days	£30
Toxicology	Turn round	Cost
Caffeine & Paraxanthine	1-2 hours	£20
CDT	5 days	£40
Ethanol	1-2 hours	£30
Ethylene/Diethylene Glycol	1-2 hours	£200
	Out of hours:	£350
Methanol (methyl alcohol)	1-2 hours	£75
	Out of hours:	£150
Sulphonyl Urea, Antidiabetic Drug Screen	2-3 hours	£90
Tricyclic Antidepressants (Total) by Immunoassay	1-2 hours	£60
Unknown Drug Screen	2-3 hours	£300
LC-QTOF Screen	1 day	£80
Paraquat		£90
Diaquat		£90
Urine Diuretic Screen	1-2 days	£90
Urine Laxative Screen	2-3 days	£90
β-Hydroxy-Butyrate (BHB)	2-3 days	£90
γ-Hydroxy-Butyrate (GHB)	2-3 days	£90
Spiked Drink Screen	1-2 days	£250

Drugs of abuse screen	Turn round	Cost
Saliva Collection Device (pack of 20)		£30
Oral Fluid Reply Paid Kits (pack of 20)		£120
Oral Fluid	1-2 days	£20
Urine	1-2 days	£20

Current drugs of abuse panel*	
Opiates	Morphine
	DHC
	Codeine
	Heroin (6-MAM)
Opioids	Buprenorphine & Norbuprenorphine (metabolite)
	Methadone & EDDP (metabolite)
	Thebaine (poppy seed marker)
Amfetamines	Amfetamine
	Metamfetamine
	Ecstasy MDMA
	Ecstasy MDA
Ecstasy MDEA	
Cocaine	Cocaine metabolite
	Benzoyllecgonine
Benzodiazepines	Lorazepam
	Oxazepam
	Temazepam
	Nordiazepam
	Diazepam
Street highs	Methylenedioxypyrovalerone (MDPV, bath salts)
	4-methylethcathinone (4-MEC, NRG-2)
	Mephedrone (Meow, meow)
	Cathinone (Khat)
Other drugs	PCP
	Ketamine
	Tramadol

*Includes classic drugs of abuse & newer 'street highs' For medico-legal work, where a quantitation of positive results is required in addition to the screen, charges are £70.

Other drugs of abuse screening	Turn round	Cost
Amfetamine ratio (resolution of D, L isomers)	1 day	£40
Barbiturates	1 day	£60
Cannabis Screen	1 day	£15
Screen & Confirmation		£35
Other drugs detectable on the LC-QTOF	1 day	£80

Immunology	Turn round	Cost
ISAC (Specific IgE allergen component panel)	14-21 days	£180
Specific IgE single common allergen	3-5 days	£14
Specific IgE single rare allergen	3-5 days	£15
Specific IgE Mixed panel	3-5 days	£15.50
Specific IgE to Mixed Food	3-5 days	£18.50
Specific IgE Bee Venom Apim1	3-5 days	£15
Specific IgE Birch, rBetv1	3-5 days	£15
Specific IgE Egg Gald1	3-5 days	£15



Cheryl Powell and Nazleen Musood working in our Immunology Laboratory



Immunology continued	Turn round	Cost
Specific IgE Grass – rPhl p7,p12	3-5 days	£15
Specific IgE Hazelnut – Cora1/Cora8	3-5 days	£22
Specific IgE Latex HevB1, B3, B5, B6.01, B6.02, B8	3-5 days	£65
Specific IgE Peanut Arah1,2,3,8, 9	3-5 days	£55
Specific IgE Wasp Vesv5	3-5 days	£15
Specific IgE Wheat Omega5 gliadin	3-5 days	£15
Total IgE	3-5 days	£13
Tryptase	3-5 days	£20
CCP abs	3-5 days	£10
Avian IgG - budgie	3-7 days	£13
Avian IgG - pigeon	3-7 days	£13
Aspergillus IgG	3-7 days	£11
Glomerular Basement Membrane (GBM) abs	3-5 days	£12
Complement C3	1-2 days	£10
Complement C4	1-2 days	£10
Rheumatoid factor	1-2 days	£6
IGG1, IGG2, IGG3 & IGG4	3-7 days	£28
C1 Inhibitor	3-7 days	£9
Beta 2 Microglobulin	3-7 days	£7
Tissue Transglutaminase (IgA) abs	2-4 days	£10
Myeloperoxidase (MPO) abs & Proteinase 3 (PR3) abs	3-7 days	£30
Double stranded DNA quantitation abs	1-7 days	£11
IgG/IgM Cardioliipin abs screen	3-7 days	£14
IgG Cardioliipin abs	3-7 days	£6
IgM Cardioliipin abs	3-7 days	£6
ENA Screen	3-7 days	£10
ENA Profile	10-14 days	£22
Thyroid Peroxidase abs (TPO)	3-7 days	£10
Intrinsic Factor abs	3-7 days	£10
HIB abs	10-14 days	£10.50
Tetanus abs	10-14 days	£10.50
Pneumococcal ABS	10-14 days	£13
GAD abs	10-20 days	£16
Anti-nuclear antibodies	1-3 days	£10
Anti-nuclear antibodies titration	1-3 days	£11.50
Mitochondrial abs	3-5 days	£10
Smooth Muscle abs	3-5 days	£10
Gastric Parietal cell abs	3-5 days	£10
Liver Kidney Microsomal abs	3-5 days	£10
Mitochondrial abs quantitation	3-7 days	£15
Smooth Muscle abs quantitation	3-7 days	£15
Endomysial (IgA) abs	3-5 days	£13.50
ANCA abs	1-2 days	£10
Double Stranded dsDNA screen	1-3 days	£7.50
Epidermal abs	3-7 days	£12
Anti-C1INH abs	up to 28 days	£180
T spot	24 hours after sample receipt	£75

Immunology Referral Testing Services

Our Immunology Laboratory is now joining with the cityassays.org.uk brand to offer a number of tests to other Trusts.

Our Immunology Department has three Consultants who as well as running a busy clinical service also take a very active part in ensuring that our Immunology laboratory is offering excellent routine services, along with innovation of relevant new tests. This service has recently moved to our new Sandwell Blood Sciences Laboratory facilities.

Key Ares for SWBH Immunology Innovations:

ISAC/Specific IgE Component Testing

We offer a service for IgE to various purified allergen components either as individual components associated with a specific allergen or as a 112 allergen array using Immuno- Solid Phase Chip (ISAC).

ISAC is the only in vitro diagnostic test for simultaneous measurement of specific IgE antibodies to a broad spectrum of allergen components.

This test provides results to 112 components from 51 allergen sources. A full interpretive report is provided with all results.

In addition to ISAC, we are also able to offer testing to individual components. The current repertoire is:

Current CRD Repertoire

Peanut	rArah1,2,3,8 and 9.
Hazelnut	Cora1 and Cora8
Egg	Ovomucoid (Gald1)
Latex	Hev b1, 3, 5, 6.01, 6.02 and 8
Grass	profilinsrPhl 7, p12
Bee venom	Apim1
Wasp venom	Vesv5
Birch	rBetv1 PR10

Anti-C1INH antibodies

We provide a service to measure antibodies to C1 Inhibitor. These antibodies can arise in patients with B cell lymphoproliferative disease, connective tissue disease and with certain solid tumours.

For further details please contact the Immunology Laboratory Manager, Helen Sandy
Email: Helen.sandy@nhs.net
Tel : 0121 507 4258



Shabir Rajpar (Deputy Manager), Sadia Noorani (Consultant Immunologist & Head of Department) and Helen Sandy (Immunology Manager)

Vitamin D Deficiency in Pregnancy

The Vitamin Laboratory continues to grow with nearly 80,000 samples received for serum vitamin D analysis last year. Our blood spot vitamin D service has also gone from strength to strength, with samples being received from all over the UK and around the world.

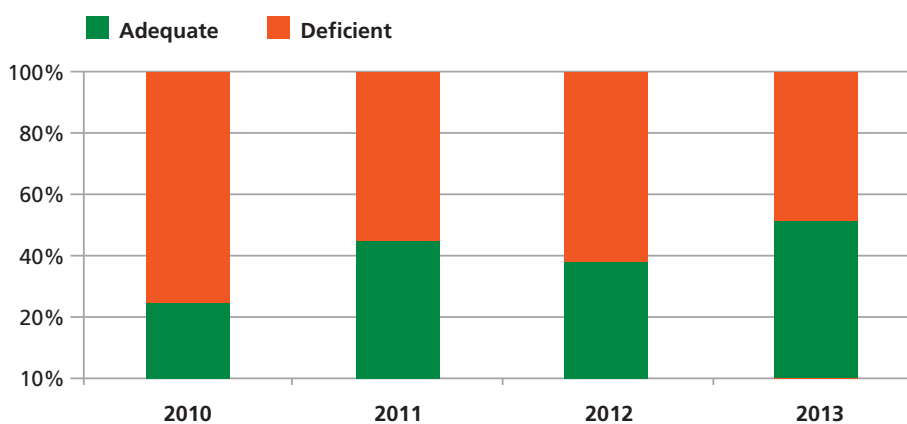
Over the last four years we have measured serum 25-hydroxy vitamin D (25OHD) levels in samples sent in for Downs screening in pregnant women during the Autumn. Our work has shown a staggering number of women have severe deficiency (total 25OHD < 15 nmol/L). In 2010, 13.7% of the women had severe deficiency, but interestingly this has dropped by over half to 6.2% by 2013. When the data is broken down by ethnicity, the situation is even worse for Asian women, with 22.1% showing severe deficiency in 2010 and only 13.2% of them showing adequate levels (total 25OHD > 50 nmol/L). However, in 2013 this has dropped as only 10.5% of Asian women had severely deficient levels, while 39.5% had adequate levels.

Improving the Picture

So, the picture does appear to be improving as in 2010 only 24% of women showed an adequate level of 25OHD, but this had risen to 51.2% by 2013. This may be as a result of the increased awareness of the importance of vitamin D supplementation during pregnancy brought about by the Healthy Start scheme, which since 2011 has provided free vitamin D supplements to all pregnant women.

Despite these improvements our data has shown an unacceptably high proportion of pregnant women in inner city Birmingham have a less than adequate 25OHD status, especially those from ethnic minorities. This raises the questions of whether enough pregnant women are taking supplements, or if they are taking the supplements, is the level of supplementation enough to increase their levels into the adequate status?

Changes in the Vitamin D Status of pregnant women from 2010 to 2013



cityassays.org.uk

Our website gives basic details for many of our tests.



This includes:

- Downloadable PDF files of user information leaflets
- Relevant information and background details
- Up to date turn round times



Electronic Result Transfer between Laboratories

Over the coming months we are planning to implement the National Pathology Exchange (Npex). This will enable us to send results to other labs that have this system by electronic means. We already have electronic reporting in the form of secure PDF reports sent by email. If you are unable to have full electronic results from us then please do consider the alternative of PDF email reporting.

For further details on these then please contact Raj Garcha at Email: rajvindergarcha@nhs.net

What a Twitter...



Follow us: @Cityassays

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