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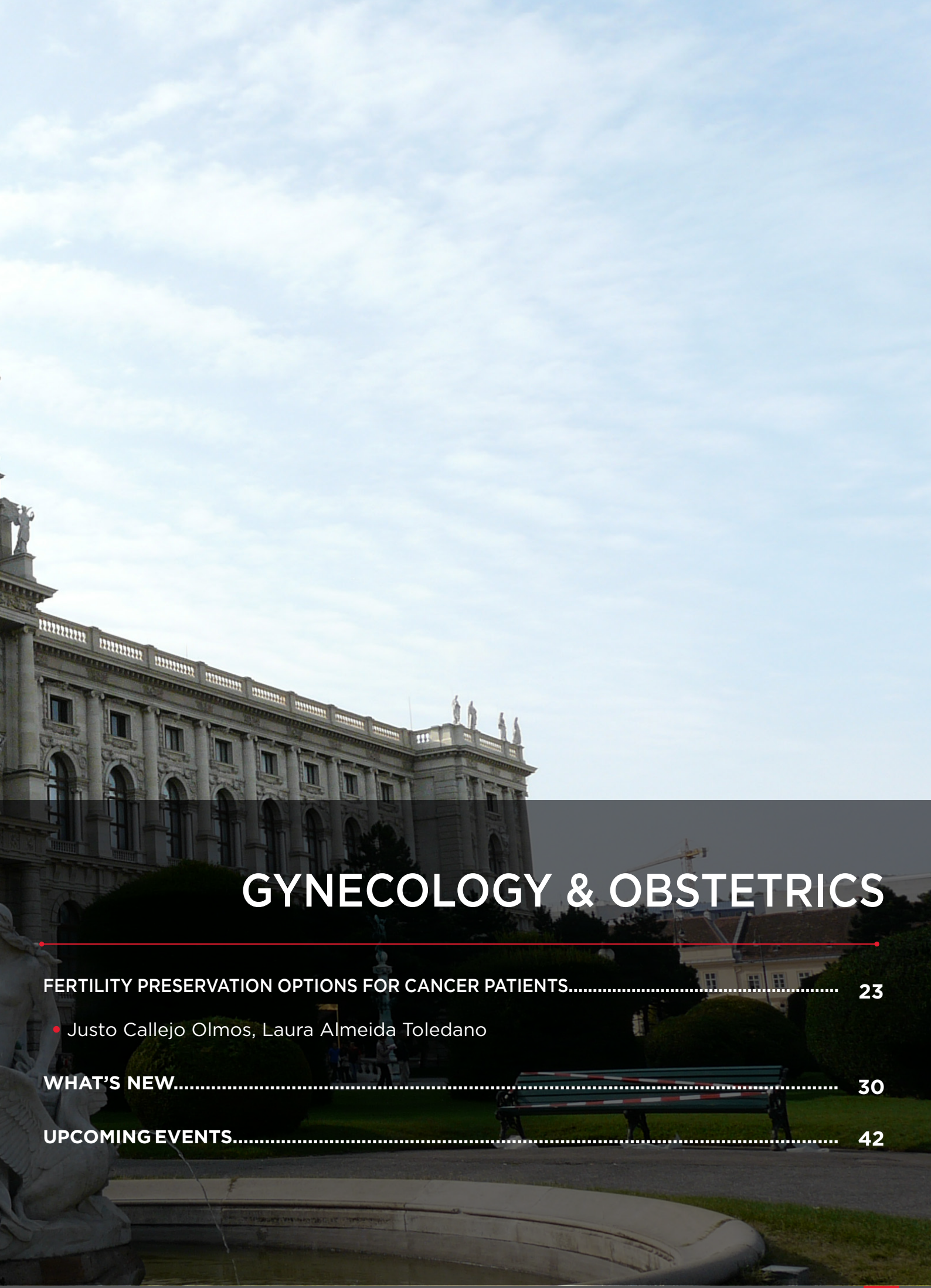

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Welcome

Kelly-Ann Lazarus

Editor, European Medical Journal

We are very excited to launch the second edition of *EMJ - Gynecology and Obstetrics*. Following feedback received from our first edition, we are happy to present our new and improved journal, packed with exciting high-calibre articles and news updates in the field of gynecology and obstetrics.

When a new baby arrives there is much to celebrate, but for many women conceiving can be a difficult and emotional process. In our 'What's New' section, findings of a study by Dr Elisabeth Juul Gade are presented in which women who are affected by asthma experience a prolonged time to pregnancy, compared to their non-asthmatic counterparts.

Another impact on pregnancy outcomes is ethnicity. Data have shown that more white European women gave birth to a live baby after fertility treatment compared to ethnic women. While more research is needed, this study is important in understanding how ethnicity can be an indicator for successful fertility treatment.

Dr Justo Callejo Olmos also explored different fertility preservation techniques in his article: 'Fertility preservation options for cancer patients'. One of the adverse effects of cancer treatments can be premature ovarian failure which ultimately has an impact on a woman's reproductive capacity. The article explores the various different fertility preservation techniques, aiming to take a more personalised approach, in which the authors suggest that combining various treatments may be beneficial.

Also included in this edition, is a very enlightening article written by Dr Gill Thomson, entitled: 'What works for breastfeeding peer support: Time to get real?' The article takes an individual approach towards peer-breastfeeding; the paper emphasises the principal that both policy makers and researchers should take an individualised approach and try and answer the questions: 'What works for whom, in what circumstances, in what respects, and how?'

For a new mother, breastfeeding can seem, at times, to be a both daunting and frustrating experience, but numerous studies have proven that 'breast is best'. A study group from the US have emphasised that the benefits of breastfeeding extend further than previously thought. In fact, if there are insufficient levels of insulin-like growth factor in the baby, a possible biomarker for autism, this protein could be received though breastfeeding.

On behalf of myself, and the team here at EMJ, I hope that you enjoy this publication, and would like to wish all of our readers, authors, and Editorial Board members a very merry Christmas and a prosperous 2014.

Kelly-Ann Lazarus

Editor, European Medical Journal

AN OVERVIEW OF CLINICAL AND PHYSIOPATHOLOGICAL FEATURES OF THROMBOTIC THROMBOCYTOPENIC PURPURA DURING PREGNANCY

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP), haemolytic-uraemic syndrome (HUS), preeclampsia-HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, and some other autoimmune syndromes like catastrophic antiphospholipid syndrome (CAPS), are microangiopathic disorders that can be diagnosed during pregnancy. Although the underlying physiopathological mechanisms differ, the clinical consequences are very similar in all of them, so that it is very difficult to establish a differential diagnosis. Since each disease has its own treatment particularities, and maternal and perinatal morbidity and mortality are high when treatment is not appropriate, gynaecologists need to have a thorough understanding of differentiating characteristics of these disorders. TTP is more common in women, with a peak incidence in the fourth decade of life, and 10% of all cases occur during pregnancy. In the absence of adequate diagnosis and treatment, the maternal and foetal mortality rate approaches 90%. Preconceptional counselling should be provided to women with prior episodes of TTP or congenial Upshaw-Schülman syndrome.

Keywords: Thrombotic thrombocytopenic purpura, high-risk pregnancy, plasma exchange, plasmapheresis, perinatal mortality, maternal mortality.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is one of the microangiopathic disorders that can be diagnosed during pregnancy. These alterations are characterised by the formation of microthrombi in small vessels, leading to thrombocytopenia, microangiopathic haemolytic anaemia, and multiple organ damage. The hypercoagulability state observed during pregnancy conditions the incidence of such disorders in pregnant women compared with the general population. Specifically, these disorders comprise TTP, haemolytic-uraemic syndrome (HUS), preeclampsia-HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, and some other autoimmune diseases like catastrophic antiphospholipid syndrome (CAPS).

TTP is clinically characterised by a group of five symptoms: thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological alterations, and renal failure. It can exhibit a familial trait, though idiopathic TTP is the most common presentation. HUS in turn is characterised by renal failure, and although it is typically observed in children with a history of infection due to toxin-producing bacteria in the previous days or weeks, the disease occasionally has also been reported during pregnancy. On the other hand, both preeclampsia and HELLP syndrome belong to a range of disorders in which arterial hypertension is the fundamental clinical feature - HELLP syndrome being one of the most serious conditions. On the other hand, CAPS is a serious and rapidly progressive form of antiphospholipid syndrome leading to multiple

organ failure. CAPS may be the first manifestation of the disease, although previous history of antiphospholipid syndrome, systemic lupus erythematosus, or in a small number of cases, Sjögren's syndrome or systemic sclerosis, could guide the doctor. In CAPS, the activation of coagulation is caused by the presence of autoantibodies that bind to membrane phospholipids.

Although the underlying physiopathological mechanisms differ, the clinical consequences are very similar. This makes it very difficult to establish a differential diagnosis. Each disease has its own treatment particularities, and maternal and perinatal morbidity and mortality are high when treatment is not appropriate. It is therefore necessary for gynaecologists to have a thorough understanding of differentiating characteristics of these disorders.

Epidemiology and Presentations

The reported incidence[1] of TTP in the general population is 3.8 cases per million individuals. In turn, the incidence of TTP and HUS, as disorders differentiated on the basis of laboratory test criteria, is one case in every 25,000 pregnancies[2] and one case in every 198,000 pregnancies,[3] respectively. TTP is more common in women, with a peak incidence in the fourth decade of life, and 10% of all cases occur during pregnancy.[4] The incidence of TTP shows a female/male ratio of 3:2, possibly because of the greater female susceptibility towards autoimmune disorders. Pregnancy triggers both the appearance of the disease and its recurrence.[5] TTP associated to pregnancy accounts for 10-30% of all cases of TTP diagnosed in adults.[6,7]

TTP can manifest in three clinical forms. One form is familial-hereditary congenital disease or Upshaw Schülman syndrome (SUS), which accounts for a mere 5% of all cases in the general population and 24% of all cases associated with pregnancy,[3] while a second form is acquired idiopathic disease (the most frequent presentation), and a third form is related to use of drugs, infections, neoplasms, and pregnancy. The disease often evolves in the form of outbreaks. In this sense, following remission of the initial episode, recurrences of the clinical symptoms are typically observed, particularly during the first year after the diagnosis.[8]

The inclusion, in some series of pregnant women with minor forms of TTP or with probable HELLP syndrome, results in reported[9] maternal mortality rates of <10%. However, in the absence of adequate diagnosis and treatment, the maternal and foetal mortality rate approaches 90%.[10] In this context, unlike in HELLP syndrome or severe preeclampsia, there is no evidence that uterine evacuation is able to solve the problem;[11] a correct differential diagnosis is therefore of crucial importance. TTP as either an initial episode or recurrence can manifest at any time during pregnancy,[12] though the condition is more often diagnosed in advanced gestation, during the second or third trimester, in peripartum, or even in the puerperal period.[13,14]

TTP was first described in 1924 by Eli Moschcowitz in a 16-year-old girl[15] who developed haemolytic anaemia, thrombocytopenia, neurological alterations, and impaired renal function, followed by death due to cerebral infarction and heart failure. The autopsy revealed generalised thrombosis, particularly of the terminal arterioles. The first documented case of TTP during pregnancy was reported in 1955, in a 30-year-old woman in the eighth month of pregnancy,[16] who died as a result of the disease.

PHYSIOPATHOLOGY

Von Willebrand factor (vWF) is a multimeric glycoprotein fundamentally produced in the endothelial cells, where it accumulates in the Weibel-Palade bodies, and in megakaryocytes, conforming the so-called alpha granules. These intracellular vWF multimers are larger (ultra-large multimers) than those that circulate freely in plasma under normal conditions (large multimers). The ultra-large multimers are able to bind with greater affinity than the large multimers to the platelet glycoprotein Ib (GPIb) receptors, thereby favouring platelet aggregation. Regulation of multimer size is therefore essential in order to maintain adequate function. vWF also has zones for binding to the vascular endothelium and platelets, favouring their adhesion to activated platelets, facilitating their aggregation, and to factor VIII, preventing the latter from undergoing premature degradation.[17] Regulation of multimer size is mediated by a metalloproteinase known as ADAMTS-13 (A disintegrin and metalloproteinase with a

thrombospondin type 1 motif, member 13) that cleaves the ultra-large multimers as they are secreted, converting them into chains that are anchored in the collagen of the vascular wall or circulate freely.[18]

Defects in degradation of the ultra-large vWF multimers give rise to the different forms of TTP. The existence of ultra-large vWF multimers in the plasma of patients with recurrent TTP was reported in 1982. These multimers would increase platelet adherence to the endothelium, particularly in high-flow vessels (capillaries), thereby favouring the appearance of thrombi.[19,20]

In the familial forms of the disease (SUS), homozygous mutation of the gene encoding for the synthesis of ADAMTS-13 (chromosome 9) causes the protease activity to drop to <5% of that seen under normal conditions.[21] The familial form usually begins to manifest during childhood, though in some cases it develops later in life, and occasionally during pregnancy. Many mutations have been identified in relation to ADAMTS-13 deficiency, with variable impact in relation to the clinical severity of the condition. Approximately 90% of all patients with both homo and heterozygous mutations present symptomatic TTP.[22,23] In the acquired forms, protease activity is either low or absent during the disease outbreaks, and recovers during the disease-free intervals. In these cases the existence of an anti-ADAMTS-13 IgG autoantibody has been identified. The production of autoantibodies may be transient and/or recurrent, thereby conditioning the course of acquired idiopathic TTP. Autoantibodies can be detected in approximately 31-38% of all patients with idiopathic TTP.

Increased circulating oestrogen levels have been related to an increase in coagulation[24] factors such as factor VIII and vWF, as well as to a decrease in the protease activity of the enzyme ADAMTS-13.[25] This circumstance is another factor giving rise to an increased incidence of TTP among women and its occurrence or relapse during pregnancy,[26] and is co-responsible for the hypercoagulability state seen during pregnancy.[27,28] A significant observation is the fact that 100% of all patients with SUS who do not receive prophylactic treatment initially develop the disease or experience recurrences during pregnancy, and an important percentage suffer their first episode upon becoming pregnant. On the other hand, 25% of all patients with acquired TTP develop recurrences during pregnancy or in the immediate puerperal period.

Despite knowledge of the mentioned physiopathological aspects of the disease, doubts remain regarding the existence of still unknown additional aetiopathogenic factors. The fact that there have been reports of cases of acquired idiopathic TTP in which the ADAMTS-13 levels are normal, or of familial TTP characterised by a complete absence of ADAMTS-13 without clinical manifestations until adult age, points to the need for further investigation of the pathogenesis of this disease.[29] Quantification of ADAMTS-13 in the disease-free intervals contributes to distinguish among the different forms of the disease. In this sense, values of <10% of normal are typical of hereditary TTP, while values >30% are indicative of acquired TTP.[3]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Between 10-40% of the patients experience pseudo-influenza syndrome in the weeks prior to diagnosis, and asthaenia, malaise, and fever for days or weeks, refractory to initial empirical symptomatic treatment, are occasionally observed. The classical group of five clinical symptoms is observed in 40% of the cases, while 75% of all patients exhibit a triad in the form of microangiopathic haemolytic anaemia, thrombocytopenia, and neurological symptoms such as headache, diminished consciousness, or seizures.[30] It is also possible to observe moderate renal dysfunction, with creatinine levels <3 mg/dL,[6] though both neurological and renal disorders are more common in the terminal stages of untreated cases. It must be also taken into account that cardiac abnormalities may be important and are often unrecognised causes of mortality and morbidity in patients with TTP.[31] Cardiac symptoms are frequently overlooked because many patients are young, without cardiac risk factors, but angina, congestive heart failure, arrhythmias, and syncope have been reported in >20% of TTP patients and myocardial infarctions appear in 24% of autopsies. In the absence of clear evidence for cardiac involvement, all TTP patients should be screened with a focused cardiac history, electrocardiogram and serial cardiac enzymes, and should be monitored.[31,32]

Table 1. Clinical and laboratory findings.

	TTP	HUS	HELLP
Hypertension (%)	20-75	80-90	85
Proteinuria (%)	With haematuria	80-90	90-95
Fever (%)	20-50	Not reported	Absent
Nausea and vomiting (%)	Common	Common	40
Abdominal pain (%)	Common	Common	60-80
Central nervous system (%)	60-70	Not reported	40-60
ADAMTS13 activity 5%	33-100	Rare	Absent
von Willebrand factor multimers (%)	80-90	90	Absent
Platelet count (mm^3)	>20.000	<20.000	<20.000
Anaemia (%)	100	100	<50
Elevated transaminases (%)	Usually absent	Usually absent	100
Elevated lactic dehydrogenase (%)	100	100	100

Adapted from Stella CL et al.[41]

Because of the need for early diagnosis and adequate treatment, the five clinical characteristics regarded as crucial for diagnosing the disease have been reduced to only two: thrombocytopenia and microangiopathic haemolytic anaemia. Thus, in daily practice, the presence of thrombocytopenia ($<20x10^9$/L), schistocytes representing >1% of the global red cell population, and lactate dehydrogenase (LDH) elevation in the absence of other apparent causes, suffice to diagnose TTP and start treatment.[33-37] Since in this way TTP is indistinguishable from HUS, some authors include both conditions under the term TTP-HUS.[38]

The role of the determination of ADAMTS-13 and ultra-large vWF multimers in characterising the different microangiopathic disorders is unclear. ADAMTS-13 activity varies between 50-78% in healthy adults, though during pregnancy the variability is usually lower, and only in cases of SUS are activity values of <5% observed. There have been reports of patients who develop an episode of TTP with ADAMTS-13 levels >50%. In turn, some patients with activity levels <5% remain disease-free,[39] and some series have reported higher mortality in cases of TTP during pregnancy than in idiopathic PTT in non-pregnant patients, independently of the ADAMTS-13 activity level.[40]

It should be mentioned that HELLP syndrome occurs in 0.5-0.9% of all pregnancies and affects 10-20% of all patients with severe preeclampsia. Both TTP and preeclampsia-HELLP syndrome occur more frequently in the second half of pregnancy, in the peripartum or postpartum. Establishing a differential diagnosis is therefore complicated since the clinical manifestations are very similar. However, while the end of pregnancy contributes to treatment in cases of preeclampsia-HELLP syndrome, the clinical course of TTP or HUS is not modified. The need for an adequate differential diagnosis has caused the diagnosis of TTP-HUS to be considered in those pregnant women who, beyond week 24, present microangiopathic haemolytic anaemia (negative indirect Coombs' test) and thrombocytopenia in the absence of arterial hypertension and/or proteinuria, as well as in pregnant women in the first or second trimester (<24 weeks) in which any of the orienting symptoms are suspected, in view of the low frequency of HELLP syndrome in these gestational weeks. The shorter the interval from symptoms onset to the start of treatment, the better the perinatal outcomes.[41]

Regarding CAPS, diagnostic criteria include: 1) evidence of involvement of three or more organs, systems and/or tissues; 2) development of events simultaneously or in less than a week; 3) pathologic confirmation of occlusion of small vessels in at least one organ or tissue, and 4) laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies).[42,43]

Table 2. Clinical criteria for diagnosis.

Severe Preeclampsia ACOG criteria (any of these findings)	• Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest • Cerebral or visual disturbances • Pulmonary oedema • Thrombocytopenia (platelets count <100x10^9/L) • Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both • Progressive renal insufficiency (serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatine concentration in the absence of other renal disease
HELLP Mississippi criteria	• Thrombocytopenia (usually <100x10^9/L with a documented prenatally normal platelet count) • Hepatic dysfunction: AST>48 IU/L, ALT>24 IU/L or LDH>164 IU/L • Evidence of intravascular haemolysis, to include a decreasing haematocrit concurrent with worsening thrombocytopenia, an increase in LDH, and/or evidence of bleeding involving intravenous sites or haematuria • No evidence of another disorder primarily causative of clinical and laboratory findings

Adapted from Pels et al.,[46] ACOG,[47] and Martin et al.[48]

On the other hand, the effects of hepatic insufficiency due to acute fatty liver of pregnancy should be considered in TTP differential diagnosis. This disorder has uncertain aetiology but inherited defects in the mitochondrial beta-oxidation of long chain fatty acids are associated. Clinical manifestations include abdominal pain, headache, nausea, vomiting, anorexia, and jaundice. The 20% is associated with preeclampsia, and very often coagulopathy secondary to severe hepatic impairment appears. Transaminases are often >300-500 IU/L.[44] Typical laboratory findings in acute fatty liver of pregnancy include bilirubin >2 mg/dL, hypocholesterolaemia <200 mg/dL, hypoglycaemia <60 mg/dL, hypofibrinogenaemia <300 mg/dL, decreased antithrombin III, and prothrombin time prolongation.[45]

TREATMENT

The initial treatment of TTP-HUS during pregnancy is no different from that indicated in the non-pregnant patient.[49] Patients with SUS benefit from prophylactic treatment with fresh plasma infusions every 2-3 weeks, according to the ADAMTS-13 activity levels.[49] TTP is potentially fatal, with a mortality rate of >90% before introduction of the current treatments. The prognosis, in terms of maternal-foetal survival rates, has improved since the 1970s with the development of treatments such as plasma transfusions and plasmapheresis. The mortality rate has dropped to approximately 10-20%, with a response in up to 90% of all cases of TTP, and healing rates of up to 80%. Plasmapheresis is the most effective treatment option and should be started as soon as possible. Even when the diagnosis is uncertain, the possible complications of TTP outweigh the risks of such treatment.[30,50] Plasma administration while plasmapheresis is started may be useful.[51] In fact, when plasma exchange cannot be started immediately, it is advisable to start the infusion of high fresh plasma doses under constant central venous pressure control in order to avoid volume overload.[52] Pregnancy does not appear to modify treatment response, though the effects upon the foetus have not been evaluated.

Plasmapheresis is able to eliminate circulating anti-ADAMTS-13 autoantibodies and ultra-large vWF multimers from plasma. The infusion of fresh plasma in turn helps restore the deficient ADAMTS-13 levels. A schematic representation of treatment for acute TTP episodes is provided

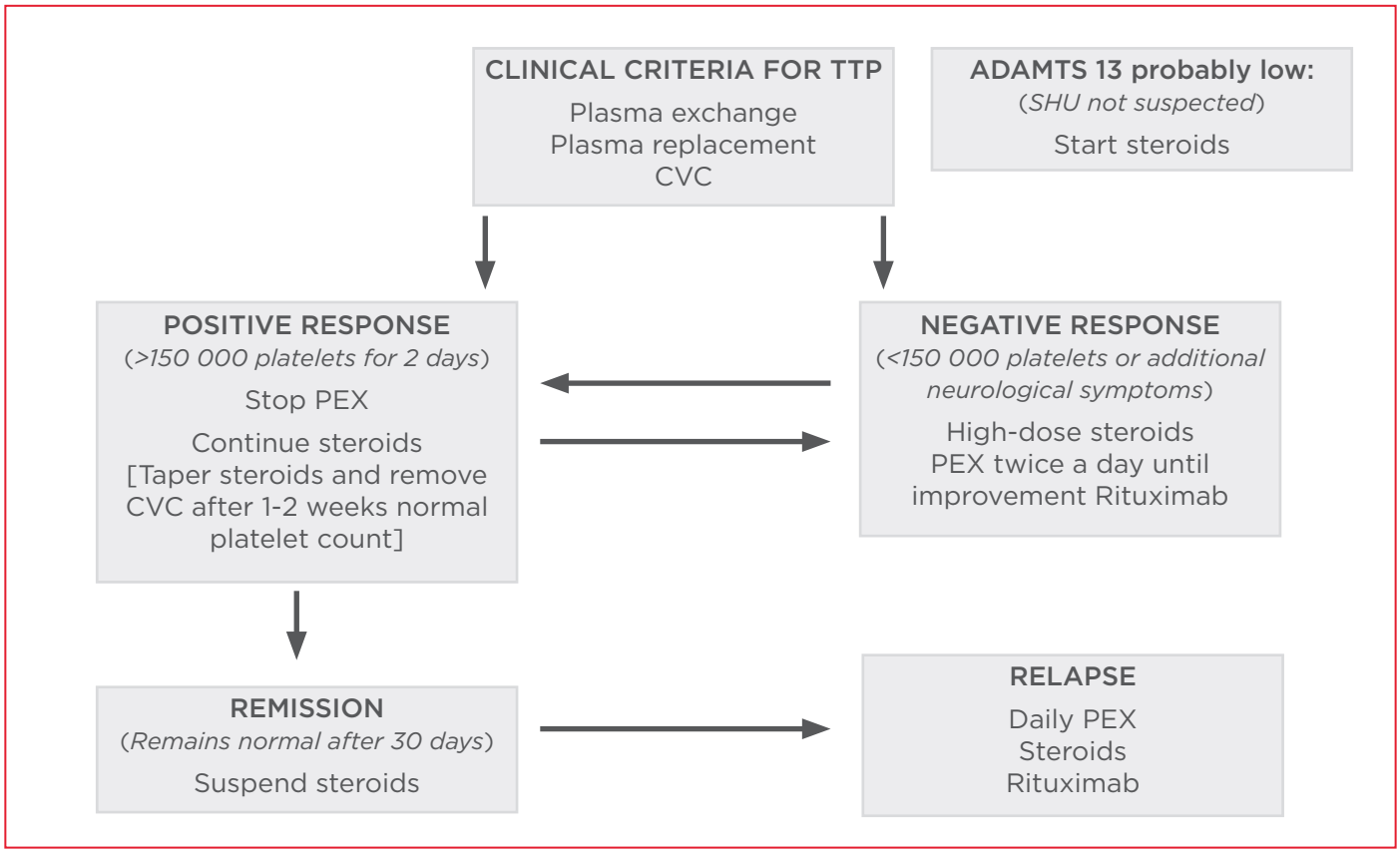

Figure 1. Schematic representation of treatment for acute TTP episodes.
PEX; plasma exchange; CVC: central venous catheter.
Adapted from George JN.[51]

in Figure 1. Corticosteroids have some effect in the treatment of TTP episodes. Before the generalised use of plasma exchange therapy, some authors reported a favourable response in 55% of the patients with neurological disorders when using high-dose corticosteroids.[53] Subsequent studies have shown the benefit of high-dose corticosteroids as adjuvant therapy (dexamethasone 10 mg/kg/day for 3 days and 2.5 mg/kg/day thereafter).[54]

Although antiplatelet treatment could seem adequate from the physiopathological perspective, some studies have found it to increase bleeding risk. The administration of antiplatelet drugs is therefore not generalised.[52] Nevertheless, some recent clinical guides suggest the administration of 75 mg/day of acetylsalicylic acid if the platelet count is >50x10^9/L.[55] The risk of venous thromboembolism has never been formally quantified in acute TTP but is likely to be increased due to immobility and acute illness. Therefore routine low molecular weight heparin (LMWH) thromboprophylaxis should be given once the platelet count has recovered to >50x10^9/l.[55,56] Platelet transfusion should be reserved for patients with life-threatening bleeding problems, since the worsened clinical condition reported by different authors after platelet transfusion suggests that it worsens microangiopathic disorder.[47] If platelet transfusion proves necessary, it should always be associated to plasma replacement therapy.[52,57]

In patients refractory to treatment (10-20% of all cases), and when exacerbations of the acute episode occur in under 30 days after normalisation of the platelet count, a monoclonal antibody (rituximab) has been shown to be effective as second-line treatment.[58] An 88% success rate has been reported with the administration of rituximab in refractory cases.[59] This monoclonal antibody allows faster recovery of the platelet count, lowers the circulating autoantibody titres, and increases ADAMTS-13 activity.[60] Rituximab is able to normalise the platelet count within an average of 2 weeks, with remission of the condition in 5 weeks, and is

effective in preventing relapse during the year following treatment. The use of rituximab during pregnancy has been associated with neonatal neutropenia, though it has been administered in the first 3 months of pregnancy without neonatal adverse effects.[61] Although some studies have reported benefits with other drugs, randomised studies are needed to clarify the role of agents such as vincristine, cyclophosphamide, or immunoglobulins via the intravenous route in the treatment of TTP in pregnancy.

PROGNOSIS

Before the introduction of plasma exchange, maternal survival in cases of TTP related to pregnancy was very limited, with a mortality rate of >90%. However, following the introduction of this treatment modality, the maternal mortality rate has dropped to 0-10%. At present, morbidity remains high, with neurological damage in up to 10% of all cases and renal damage in 21%.[61,62] In some series the perinatal mortality rate reaches[3,63] 80%, and is usually related to hypoxia due to placental vascular lesions secondary to thrombotic occlusion of the decidual arterioles. No cases of idiopathic TTP to newborn infants have been reported.

Since treatment with plasmapheresis must be started urgently after the onset of symptoms, any delay in establishing the diagnosis has negative consequences. An adequate differential diagnosis must be established between TTP and HELLP syndrome, since the treatment in each case differs, and confusing the two diseases has been associated with increased maternal mortality.[64,65] The ending of pregnancy does not improve the course of TTP. It therefore should only be performed when there is evidence of foetal distress or growth retardation, concurrent preeclampsia, or in cases where plasma exchange proves ineffective. Perimortem caesarean delivery has been described in patients with TTP following irreversible cardiorespiratory arrest.[66]

The risk of relapse in subsequent pregnancies in the case of hereditary TTP is 100% in the absence of plasma-based preventive treatment. The latter therefore must be started as soon as possible in the first trimester.[67] The risk of relapse in a subsequent pregnancy in women with acquired idiopathic TTP associated to severe ADAMTS-13 deficiency is relatively low (close to 20%).[49] Therefore, with appropriate prenatal management and correct planning, future pregnancy in patients with antecedents of TTP is reasonably safe.

The general recommendation for controlling pregnancies of this kind is to closely monitor the patients during pregnancy and start prophylactic plasmapheresis every 2 weeks if the ADAMTS-13 activity falls to under 10% or blood smears yield unequivocal evidence of red cell fragmentation (schistocytes), suggesting the presence of haemolytic anaemia.[41] Plasmapheresis is recommended before delivery. The management of patients with TTP during pregnancy should be established on an individualised basis. As a general rule it is accepted that if a patient with a prior diagnosis of TTP becomes pregnant, a first test of ADAMTS-13 activity is useful. In this way plasma exchange can be indicated if necessary, with adoption of the necessary controls.

On the other hand, pregnant or puerperal women who develop severe thrombocytopenia (<50x10^9/L) as a component of HELLP syndrome may benefit from rapid ADAMTS-13 activity testing to determine whether urgent plasma exchange could offer benefit instead of other methods, since none of the published series have found HELLP to be associated with severe ADAMTS-13 deficiency. The LDH/glutamic-oxaloacetic transaminase (GOT) ratio is very high in cases of TTP, since the LDH levels are far higher than in HELLP syndrome, while GOT is only slightly elevated. On the other hand, if a patient diagnosed with HELLP syndrome is unable to reach platelet counts >25x10^9/L after 8-12 hours of treatment with dexamethasone 10 mg, it is prudent to assume a diagnosis of TTP.[13]

According to the recent clinical guides (Grade IA recommendation), mothers with congenital TTP should visit a specialised centre to receive ADAMTS-13 through the infusion of fresh plasma on a regular basis throughout pregnancy and during puerperium if necessary.[55] Close coordination between haematologists and obstetricians with an interest in maternal-foetal medicine is required in patients with TTP (Grade IA recommendation). Counselling before conception is very important, providing information about the risks posed by pregnancy as a relapse-triggering factor (Grade IIB recommendation).[55]

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WHAT WORKS FOR BREASTFEEDING PEER SUPPORT: TIME TO GET REAL?

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ABSTRACT

Policymakers from developed countries who are looking to commission breastfeeding peer support (BPS) services have every cause to be puzzled as to whether or not they can improve continuation rates. On the one hand, BPS interventions are internationally recognised as having the potential to contribute to improving breastfeeding durations.[1] A recent Cochrane review found that additional support from lay and professional supporters can have an impact on rates,[2] and UK-based qualitative studies suggest that BPS can encourage and enable women to breastfeed for longer periods.[3,4] In the UK, peer support for breastfeeding forms part of NHS commissioning guidance.[5] On the other hand, a recent meta-regression of BPS randomised controlled trials (RCTs) found little evidence that BPS interventions improve breastfeeding durations in high-income countries[6] and concluded that peer support for breastfeeding was 'unlikely to be effective' in the UK. This paper highlights issues of intervention design and implementation that problematise interpretation of trial data drawn from the meta-regression analysis within high income countries. The paper then goes on to consider the potential for alternative approaches to review evidence for BPS, highlighting the need to integrate insights from qualitative research studies. Drawing on findings of a preliminary scoping review, we make the case for a shift towards a realist interpretation of the evidence base. We argue that a realist approach would allow findings emergent from different methodological traditions to be meaningfully integrated and the theoretical basis for BPS to be explored and tested through the construction of context-mechanism-outcome configurations. We believe this will provide a firmer basis for future intervention design and for the development of theoretically-driven evaluation studies, leading to improved clarity for delivery organisations and commissioning agencies. We contend that policy makers and researchers need to stop merely asking 'does BPS work?' and look towards approaches which enlighten 'what works for whom, in what circumstances, in what respects, and how?'[7]

Keywords: Breastfeeding, peer support, realist review, interventions.

BACKGROUND

Peer support is broadly defined as 'the provision of emotional, appraisal, and informational assistance by a created social network member who possesses experiential knowledge of a specific behaviour or stressor and similar characteristics as the target population.'[8] It is an intervention that has been applied to a wide range of health topics as a complement to existing health services.

The World Health Organization's (WHO) Global Strategy for Infant and Young Child Feeding, which aims to improve rates for breastfeeding initiation, duration and exclusivity, recommends that national governments develop a network of community-based mother-to-mother breastfeeding support groups and 'lay and peer counsellors' to enhance existing services.[1] The WHO's recommendation receives support from a recently updated Cochrane review based on 52

randomised controlled trials (RCTs and quasi-RCTs) including 37 from high-income countries, which considered the impact of 'extra support' on breastfeeding duration and exclusivity compared with 'usual maternity care.'[2] The included studies of 'extra support' evaluated the impact of additional voluntary or professional supporters working in a designated support role, as well as organisational measures such as additional staff training. The review found that extra support, whether offered by professionals, by lay or peer supporters, or by both, had a positive effect on breastfeeding duration rates. The review indicated that extra support was likely to be more effective in settings with high initiation rates, when delivered face-to-face, when offered proactively, when offered on an on-going scheduled basis, and when tailored to the needs of the population base.[2]

A recent meta-regression undertaken by Jolly et al.[6] focused more narrowly on RCTs of breastfeeding peer support (BPS) interventions, using a narrower definition of BPS as: 'Support offered by women who have received appropriate training and either have themselves breastfed or have the same socio-economic background, ethnicity, or locality as the women they are supporting. Peer supporters may be voluntary or receive basic remuneration.'[6] This review included 17 studies, 15 of which were judged to have data suitable for quantitative synthesis. This analysis separately considered the combined effect of three elements of heterogeneity among the trials: three levels of 'country-level income', two levels of 'intensity of intervention' and a binary categorisation as to whether or not the BPS intervention included antenatal contact. The results indicated that the BPS effectiveness varies according to the income level of the country; BPS interventions were found to be likely to increase breastfeeding continuation, especially exclusive breastfeeding in low or middle income countries (where their potential to make a major contribution to health outcomes is high), but had less impact in high-income countries (and were ineffective in the UK). The meta-regression indicated that less intensive interventions (<5 planned contacts) had no impact on breastfeeding duration, and whilst postnatal-only interventions were associated with improved breastfeeding durations, those that combined antenatal and postnatal contact were not.

The primary explanation advanced by Jolly et al.[6] for lowered effectiveness of BPS interventions in high-income countries is that it is difficult for BPS to deliver additional benefit over and above pre-existing systems of postnatal care (for example, in the UK through postnatal visits provided by midwives and a visit from a health visitor at 10-14 days).[6] This seems intuitively reasonable as a partial explanation of the differences; it may well be easier for BPS to demonstrate an impact when it constitutes a jump from 'virtually no support' to 'some support', as compared to a shift from 'some support' to 'some more support'. However, for the UK at least, as a full explanation this sits uneasily with longitudinal survey data which indicate very frequent unplanned breastfeeding discontinuation. In the first 6 weeks after birth, around one-third of mothers who initiate breastfeeding stop, with 80% of those who discontinue breastfeeding, stopping before they had planned to do so.[9] The explanation is also incongruent with findings from a UK service-user survey which indicated that mothers frequently have poor experiences of postnatal help with breastfeeding.[10] There does seem to be a considerable 'support gap' despite the existing framework for care in the UK. The authors of the meta-analysis note a possible alternative explanation that 'some confounding of setting by intensity of support may exist,'[6] in particular, UK-based interventions, which demonstrated no significant effect on breastfeeding duration and involved fewer than five planned contacts between peer supporter and mother.

As Hoddinott et al.[11] have discussed in their review of UK-based breastfeeding support studies, there are reasons to restrain our pessimism about the potential for interventions to be effective in high-income countries; and despite apparently contradictory findings, in the UK at least, BPS remains a recommended policy tool.[4,12,13] In practice a large number of projects exhibiting considerable heterogeneity are currently being delivered by a range of organisations.[14] Nonetheless, commissioners currently face the challenge of deciding which models should be supported, with some commissioners currently reviewing BPS provision with a view to possible disinvestment.[15] Meta-regression is intended to be hypothesis generating and whilst it has some advantages over traditional meta-analysis in enabling a limited number of aspects of heterogeneity to be included,

relationships identified through meta-regression cannot be taken as proof of causality;[16] the findings from meta-analysis can only be an indicative basis for decision-making around future intervention design.

AIMS AND APPROACHES TO THE LITERATURE

We aimed to identify issues relating to interpretation of trial data, to highlight insights from qualitative research studies that might inform the development of intervention theory, and to consider the potential for alternative approaches to review evidence for BPS. We undertook a scoping review of BPS studies in order to 'map relevant literature in the field of interest.'[17] This approach to the evidence base was sufficient for our purpose as a broad research question was being utilised (e.g. evidence for BPS) and it was being undertaken to inform whether a more systematic approach is warranted.[17] In line with the aim and purpose of this approach, a formal quality appraisal of included literature was not undertaken,[17] rather we reviewed and considered each paper for inclusion based on concepts of relevance and rigour.[7] Finally, we considered whether realist approaches would be helpful in overcoming any methodological and theoretical gaps in the existing evidence base.

ISSUES IN THE INTERPRETATION OF BPS TRIAL DATA

Our re-reading of existing BPS RCTs suggests that there are five areas of difficulty that need to be considered when interpreting trial data. First, these include issues relating to study design (for example, a lack of study power evident within a number of the trials, possible contamination across trial arms, and losses to follow-up).[6] Second, several RCTs failed to implement the intervention as planned. The convention for RCTs and meta-regression is to analyse on intention to treat; any failure to implement the intervention as planned or poor reporting of implementation is therefore relevant to the interpretation of the findings (six trials included in meta-regression did not report the number of contacts provided, nor overall uptake of the intervention).[6] Third, there are issues relating to the intended design of trialled interventions which need careful consideration; in retrospect it seems hardly surprising that interventions that are predominantly reactive in the postnatal period (so that the mother is primarily responsible for seeking out help)[18,19] or that only initiated contact 3 months after the birth of the baby[20] did not 'work'.

Fourth, despite attempts through meta-regression to stratify findings by country-setting, intervention intensity and timing, existing reviews indicate that multiple aspects of heterogeneity remain unconsidered.[6,11]

Key areas of variation described in study papers but not considered through meta-regression include differences in target populations (income level, ethnicity, previous breastfeeding experience, and motivation to breastfeed); characteristics and training of peer supporters (degree of similarity to target population, length, underpinning philosophy and provenance of peer supporter training, and ongoing supervision arrangements); degree to which the programme was delivered on a proactive or reactive basis; how the intervention was delivered (telephone and/or face-to-face), and where the intervention was delivered (home, clinic, hospital, multi-setting). Further consideration indicates that the three dimensions of difference that were incorporated into the meta-regression require additional exploration. Several interventions in high-income countries are targeted towards low-income or marginalised populations living in those countries; is it the country setting or the relative income of the target population within that country which matter most? What is the 'minimum' intensity for effective intervention, and should the level of intensity vary along the mother's feeding journey? Is BPS intervention in the immediate postnatal period particularly important? As others have noted, descriptions of programme theory, which might provide an underpinning rationale for chosen components of intervention, are frequently absent within the descriptions of trials,[21] so that mechanisms for change are often implied rather than explicit.

Fifth, BPS is a quintessential example of a complex intervention. This is true in the straightforward sense of being complicated, incorporating relationships between dynamic components and the need for different aspects of the intervention design to work in conjunction with one another. These components also include the recipient/provider, components of

the existing intervention setting and multiple delivery partners, and between the intervention and issues relating to a wider context such as Baby Friendly Hospital Initiative status[22] or country-level compliance with the WHO code. Furthermore, BPS interventions are complex in the true sense that the intervention itself might be expected to lead to unanticipated emergent structures within an existing delivery environment (for example, through the development of new partnership arrangements as the intervention progresses), which in turn may have consequences on effectiveness.[23] Prospective evaluation alongside a trial of a professional-led intervention to explore the impact of breastfeeding support groups by Hoddinott et al.[24] indicated key contextual factors as to why the trial was ineffective in certain areas, including deprivation of the target group and inter-professional barriers. By contrast, in areas where breastfeeding rates rose there was evidence of leadership, multi-disciplinary working, and reflective action cycles.

INSIGHTS FROM QUALITATIVE STUDIES OF BPS

Qualitative studies of BPS provide insight into participants' own understandings as to why interventions may, or may not, be effective within particular contexts and which components of interventions work in favour or against outcomes. These insights therefore provide a rich resource for theory building. A meta-synthesis of research on perceptions of breastfeeding support, drawn from 31 primary research qualitative and survey studies identified through systematic review, suggests that the character of the relationship between peer supporter and mother may be an important component for peer support intervention design.[25] This review found that breastfeeding support occurs along a continuum from 'authentic presence' to 'disconnected encounters', and the mothers' encounters with a supporter may be experienced as 'facilitative' or as 'reductionist'. 'Authentic presence' referred to a trusting relationship and rapport between the mother and supporter, with a 'facilitative' style reflecting a partnership, with information and support tailored towards the values and needs of the woman. 'Disconnected encounters' were characterised by limited or no relationship and a lack of rapport, with a 'reductionist' approach signifying how information and advice were given in a didactic style. These findings indicate the importance of person-centred communication skills and of relationships in supporting a woman to breastfeed. The authors indicate 'continuity of carer' as a feature likely to facilitate authentic and facilitative encounters.[25] The quality of the relationship between mother and supporter remains an untested component within intervention trial data; nor do we currently have a good understanding of the context factors that can best promote supportive relationships.

Further qualitative studies that have focused on women's experiences of BPS, and which emphasised the benefits and value of this form of support, have highlighted the significance of shared experience and shared language between peer supporters and women.[3,14,26-30] Studies indicated that BPS is valued in terms of the increased social interactions; the opportunities to question and discuss personal choices in relation to infant feeding as well as the emotional warmth and advocacy that peer support provides.[3,26-30] The fact that peer supporters encourage, facilitate, and enable access to group support (e.g. by accompanying women) and subsequent supportive peer networks is also positively perceived.[3,27] Whilst these studies provide valuable evidence in terms of what women value, and point to the mechanisms through which support can be effective, issues pertaining to how BPS should be delivered, when, and by whom remain unanswered.

CASE FOR A REALIST APPROACH

Researchers have suggested that further trials to assess the effectiveness (including cost-effectiveness) of BPS are warranted,[11] together with high quality evaluation to support, explore and measure the impact of the intervention.[6] In the UK this recommendation has been taken up by the National Institute of Health Research, with funding recently made available for a feasibility trial of BPS interventions (Health Technol Assessment [HTA] no. 13/18). A key challenge in understanding the varied and often apparently contradictory findings of BPS trials is the lack of clarification of the study context, nature of BPS work involved, the processes through which the scheme operates, as well as the definition or targeting of those most likely to benefit. There is also evidence to suggest that

some BPS interventions are likely to be successful in terms of sustainability[14] and outcomes[24] and are more likely to be perceived as acceptable by mothers.[25] However, these different strands of evidence have not been fully integrated to inform recommendations for intervention design.

Given the paucity of existing evidence for effectiveness in high-income countries, heterogeneity and under-theorisation, social scientists looking to expand the evidence base for BPS need to consider two related questions:

• How can we know what sorts of BPS interventions we should be testing? How can we ensure that when we design BPS interventions we incorporate the characteristics most likely to be associated with success in a given setting (and avoid components likely to be associated with failure)? How can we avoid the dangers of researchers seeking to test their favourite theory, or of commissioners opting to fund designs that have purely operational appeal?

• How should evaluation of BPS be conducted? In particular, how should the experience of implementation failure within BPS interventions inform our decisions about intervention design in the future?

We contend that applying realist approaches to assess and interpret the evidence for BPS would help to answer these questions and to provide guidance as to what sorts of interventions have the potential to create successful outcomes. Pawson and colleagues,[31] key proponents of realist approaches to evidence review and intervention evaluation, argue that because intervention programmes are embedded within a complex interplay of individual, interpersonal and institutional social systems, they can never be expected to work indefinitely in the same way, in all circumstances, for all people.[7,31] They assert that experimental research operates from the premise that like will always produce like, and that the predominant focus on outcomes in RCTs leads to failure to consider the theoretical underpinnings, contextual factors and mechanisms that enable outcomes (or not as the case may be) to occur.[7,31] The 'black box' between inputs and outcomes remains unopened.[32]

Realist review offers a theoretical-driven approach to evidence synthesis[7,31] that is particularly suited to understanding complex interventions, where the 'active ingredient' of an intervention is likely to be better understood at a theoretical level than as a specific treatment or process. This approach aims to uncover the nature of mechanisms of effect (processes that act directly to make a difference, and that can be activated either intentionally or unintentionally by those running programmes) and how they create an effect, rather than just measuring if an effect occurs or not. Furthermore, realist review explicitly sets out to examine context: the particular social conditions and circumstances in which these mechanisms operate, and which combination of mechanism and context creates the best outcomes (context+mechanism=outcome). Realist reviews have previously been used to explore the successful components of school feeding programmes,[33] participatory research,[34] and health-related lifestyle advisor roles.[35]

When undertaking a realist review, the theoretical/explanatory frameworks - the 'middle range theories' that reflect many working hypotheses - are identified. Evidence is then gathered from published quantitative, qualitative, and grey literature about the process of implementation, outcomes as well as wider contextual information relating to the individuals, interrelationships, institutions and infrastructures within and through which the intervention is delivered.[7,31] This information is subjected to appraisal and subsequently explored to identity the relationships between context (the internal and external 'backdrop' into which programmes are introduced that are relevant to the operation of the programme mechanisms including cultural, social, interpersonal, and economic factors) and an understanding of how this influences the 'mechanisms' (the processes that create specific cognitive or emotional responses to the intervention) to achieve certain outcomes. The evidence base is subsequently evaluated to identify the demi-regularities (the semi-predictable patterns or pathways of programme functioning) and assessed against the underpinning theories with adjudication between theories considered as relevant,[33] leading to development of a unified theory as to why particular kinds of interventions in particular places might be hypothesised to be effective.

As a basic example of a theoretical explanation/ middle range theory developed in this way: if a peer supporter shares the same cultural

characteristics as the woman being supported (context), this may lead the mother to wish to reinforce her sense of belonging to that group (through a mechanism of social congruence) leading to breastfeeding continuation (outcome). In this example, the mechanism of social congruence is identified as a demi-regularity, a theoretical relationship which may be common across different intervention programmes, including breastfeeding support programmes that do not necessarily involve peer supporters, or peer interventions that are not necessarily related to breastfeeding (e.g. smoking cessation, and management of depression).

High-level explanations for the success, or not, of BPS interventions are indicated in recent reviews.[2,6,11] The discussion sections of trial papers also include many theories as to why BPS works in any particular setting; these include: 'the peer supporter is able to build a supportive relationship with the mother', 'the intervention is proactive and easily accessible to the mother','the intervention is timely', and 'there is a supportive policy infrastructure at service level.' Explanations as to why BPS may not be effective include: 'difficulties in the peer-supporter/professional interface', 'other forms of support are available', 'the women who are targeted do not want to access peer support', and the 'intervention targets women who are not motivated to breastfeed.' Whilst these potential explanations are useful, there remains a lack of clarity in terms of how components of interventions that seem to enhance or diminish chances of success can be achieved or mitigated in practice. For example, what mechanisms need to be fired in order for effective peer-woman relationships to be forged, what are the important interactions between 'peer' characteristics and delivery context, and which outcomes are important and meaningful to women themselves? An in-depth realist review, drawing on published and grey literature, and bridging the gap between the evidence synthesis formats undertaken in this area,[6,25] could help to identify and substantiate the causal paths between maternal perceptions and expectations of support, characteristics of BPS and outcomes. Through a 'realist' focus on understanding why change occurs and in which conditions change is most likely to occur, the transferable lessons identified through this process could be utilised to inform future BPS interventions.

Whether or not RCTs are compatible with a realist approach to developing an evidence base for complex social interventions is currently a topic of debate. Some authors, who accept many of the arguments as to the limitations of RCTs, suggest that the philosophy of realism should not rule out experimental methods.[36] They argue that experimental methods are crucial to establishing cause-effect relationships, and propose 'realist trials' as a way to overcome the 'black box' problem of traditional RCTs. They suggest that a 'realist trial' design would involve multiple trial arms and factorial designs, combined with longitudinal qualitative data collection with a focus on seeking to validate or refute the theories that underlie interventions. Others reject the concept of a realist RCT, attesting that suggestions for improving evidence gathering through experimental designs may take some steps towards understanding social interventions as complicated but will fail to take account of the characteristics of social interventions which mark out their true complexity – non-linearity, local adaption, feedback loops, emergence, path dependence, and the role of human agency.[37]

Our view is that continuing to commission traditional RCTs without a good theoretical underpinning (achieved by applying realist principles to the existing evidence base) is unlikely to produce information that is useful to policymakers. Whether called realist trials or not, any new RCT studies need to clarify theoretical underpinnings and build on a realist appraisal of the existing evidence base. New designs should be based on context-mechanism-outcome relationships that appear to have the potential to work in particular settings with particular target populations to test and extend the theories as to why BPS works or fails in particular contexts. Prospective evaluation is more likely to be informative if it involves embedding a theoretically informed trial within a prospective realist evaluation framework as Hoddinott and colleagues[24] have done, ensuring that it is possible to simultaneously test whether a particular intervention 'works' alongside evaluating alternative theories that might be expected to explain outcomes.

CONCLUSION

As a basis for commissioning decisions, outcome data from RCTs of BPS, whether used in isolation or combined through meta-regression, are of limited value. Interpretation difficulties arise from issues of study and intervention design, implementation problems, heterogeneity, under-theorising of mechanisms, and difficulties caused by the likelihood of a complex and emergent relationships between intervention and context. Failure to integrate evidence from experimental trials with findings from qualitative studies has contributed to a failure to develop and test intervention theories, limiting our understanding of context-mechanism interactions and contributing to a cycle of poor intervention design. The message that BPS is unlikely to be effective in the UK and will have limited impact in other high-income countries appears premature.

At worst, the problems inherent in the existing trial data, particularly in UK-based studies, may be leading to overinterpretation of negative findings. It is clearly over-simplistic to view BPS as a single intervention which either works or does not work and which can be evaluated without taking full account of delivery context. Currently, there is a lack of evidence for effectiveness of BPS in the UK, but this lack needs to be considered alongside limited evidence from a handful of RCT studies that demonstrate that BPS can be successful in improving breastfeeding durations in other high-income country contexts. A full realist review may indicate contexts in which forms of BPS are relatively weak or ineffective levers for improving breastfeeding rates. However, findings from qualitative research studies, and the evidence that peer support interventions have had success in other settings, are an important reason to consider that effective context-mechanism-outcome configurations may be found for this form of intervention.

In view of the complexity within the existing evidence base, we argue that realist approaches, which have a theory-driven focus, are needed to move our understanding forward. Our view is that a realist review of the evidence for BPS needs to be undertaken in order to inform future intervention design.

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FERTILITY PRESERVATION OPTIONS FOR CANCER PATIENTS

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ABSTRACT

Survival rates for cancer patients have increased in the last few years due to improvements achieved in cancer therapies. But, these treatments produce some adverse effects. One significant effect in prepubertal and young women is premature ovarian failure which impacts on reproductive capacity. For this reason, fertility preservation techniques appear. For the last few years there has been research into new procedures that will allow women to preserve their reproductive function. Specialised groups have appeared who advise women on the best fertility preservation option, always with a personalised approach. Currently, established fertility preservation techniques are embryo cryopreservation and oocyte cryopreservation; these two procedures can be offered widely to these women. However, there are some limitations: they cannot be offered to prepubertal women, they require a time interval to carry out (not always possible in cancer treatments), and they provide a restricted number of embryos or oocytes. On account of this, some specialised centres offer other experimental techniques such as ovarian tissue cryopreservation, which can be useful in this group of patients. We also have to take into account other procedures such as *in vitro* maturation of follicles, oophoropexy or trachelectomy. Gonadotropin-releasing hormone agonists should not be offered to these women because there is no evidence of their usefulness. We must not forget that we can recommend a combination of techniques in order to optimise their fertility options. More research is still needed to find an ideal procedure that will allow a considerable number of metaphase II oocytes to be obtained to ensure a pregnancy avoiding the problems that exist with current techniques.

Keywords: Fertility preservation, embryo cryopreservation, oocyte cryopreservation, ovarian tissue transplantation, IVM, gonadotropin-releasing hormone agonists, oophoropexy, trachelectomy.

INTRODUCTION

It was in 1953 when Jerome K. Sherman, one of the American pioneers of sperm congelation, showed for the first time the capacity of frozen-thawed sperm to fertilise an oocyte and to induce its normal embryo development. During the following years there was a growing interest in the possibility of creating sperm banks, but it was not until the early 70's that the first sperm bank was inaugurated. In 1977, through California Cryobank, Cappy Rothman and Charles Sims offered for the first time the possibility of cryopreserving the sperm in male patients who were in need of a medical castration, to mitigate the negative impact on their procreation capacity. This way if they decided in the future to have children, they could retrieve their sperm to do an artificial insemination. It is at this time that we can start to discuss fertility preservation.[1]

Due to the positive results in oncologic treatments obtaining cure rates of 70-80% and the high number of female survivors after oncologic treatments in reproductive age (around 25%)[2] who suffered from the adverse effects of these treatments (premature ovarian failure [POF]), it

was considered a possibility to offer to these women a chance to preserve their fertility by the mid 90's. In this context, the early experimental studies appeared which were headed towards the cryopreservation of ovarian tissue for its subsequent implant. We expose in this paper current available updated fertility preservation techniques and some notes about future prospects in this field.

EPIDEMIOLOGY

Currently, it is estimated that cancer incidence in women of childbearing age (under 35 years) is around 4% of all malignancies diagnosed in a year, according to American statistics.[3] The most frequently diagnosed cancers in this group are breast cancer, melanoma, cervical cancer, non-Hodgkin lymphoma, and leukaemia.[4] During the last 30 years there has been an increase in the incidence of cancer of 1% in the child population and 2% in teens, especially carcinomas, lymphomas and germ cell tumours.[5] The overall increase in incidence has been accompanied fortunately by the increase in survival, due to improvements in early diagnosis and treatments. According to SEER-NCI (Surveillance Epidemiology and End Results, National Cancer Institute-US), 5-year survival of cancer patients younger than 20-years-old was 55.8% in 1975 and 83.3% in 2005.[6] European statistics show similar figures with 5-year survival rates of 73%.[7] In relation to cancer in the paediatric population, it is considered that 1 in every 640 people aged 20-39 years is a survivor of childhood cancer,[8] which means that in the future, the reproductive problems in cancer survivors will increase progressively.

EFFECTS OF GONADOTOXIC TREATMENTS ON FERTILITY

Ovarian damage is an important and undesirable effect of current cancer treatments in women. At the same time, the reduction or loss of fertility is one of the worst tolerated aspects in these patients. The impact on the ovarian reserve is related to the accelerated depletion of the primordial germ cell pool resulting from the therapies.[9] Hence the importance of quantifying and trying to predict ovarian involvement of these treatments.

The ovarian tissue, due to its characteristics, is one of the organs most sensitive to the effects of radiotherapy, and POF is the main result.[10] Ovarian damage will have a reversible or irreversible effect depending on whether the injury is complete or partial. Although the long-term result will always be POF, its clinical translation will be different depending on the time at which it occurs;[10,11] in prepubertal patients it will manifest as absent pubertal development and those patients who have already had menarche as POF. Ovarian damage and eventual POF caused by radiotherapy will depend essentially on: the age of the patient, total radiation dose received, type of radiation, fractionation of treatment, adjuvant therapy; and depending on the idiosyncrasy of the patient, the ovarian reserve will look more or less affected.[12] When applied conventionally, radiation doses of 24 Gy result in ovarian failure.[13]

Anticancer drugs may diminish the primordial follicle pool, cause ovarian atrophy and harm the ovarian blood vasculature.[14] The extent of damage is related to the patient's age, chemotherapeutic agent, and drug regimen used. Alkylating agents, which are not cell cycle-specific, confer their deleterious effects on the vast supply of primordial germ cells and carry the highest risk of ovarian failure. Antimetabolites impact the cells (granulose and oocytes) of the metabolically active ovarian follicles and are considered to be low-risk for gonadal dysfunction, whereas cisplatin appears to carry intermediate-risk between the antimetabolites and alkylating agents.[15] On the other hand, patients who undergo bone marrow transplantation have extremely high ovarian failure rates, ranging from 72% to 100%.[12] Women over 40-years-old have a 90% chance of amenorrhea subsequent to multiagent chemotherapy, whereas the potential for POF in younger patients varies between 20% and 90%.[16]

FERTILITY PRESERVATION

The American Society of Clinical Oncology (ASCO) recommendation on fertility preservation in cancer patients indicates that all patients susceptible to treatment with radiotherapy or chemotherapy should be informed and provided with counselling depending on age, disease, prognosis, and interval time for freezing. The urgency to begin cancer treatment should not be an excuse to approach fertility preservation options.[3] Currently, embryo and oocyte cryopreservation are considered standard

Table 1. Fertility preservation techniques.

Chemoprophylaxis	Surgical procedures	Cryopreservation
GnRHa*	Oophoropexy	Embryo cryopreservation
	Trachelectomy	Oocyte cryopreservation
		Ovarian tissue cryopreservation
		IVM

*Currently, no evidence to recommend as a fertility preservation method.
GnRHa: Gonadotropin-releasing hormone agonists; IVM: *in vitro* maturation.

practice and are widely available; other fertility preservation methods should be considered experimental and only performed by providers with the necessary expertise.[17]

Gonadotropin-Releasing Hormone Agonists (GnRHa)

Assuming that turning off the reproductive axis would make the ovary less vulnerable to cytotoxic damage; it had been proposed that GnRHa could be used as ovarian protectors during gonadotoxic therapies.[18] There are several possible mechanisms thorough which GnRHa may protect the ovary during chemotherapy: reduced levels of gonadotropins, a direct influence of GnRHa on the ovary, and reduced blood flow to the ovary.

In a recent review including a total of 579 women from 12 studies, among 345 women that reported an ovarian function after the administration of GnRHa concomitant with chemotherapy, Beck-Fruchter et al.[19] found insufficient evidence to show that GnRHa co-treatment is effective in protecting the ovary from the damage of chemotherapy.

Behringer et al.[20] had to prematurely close a study on a group of women aged 18-40 years who were affected by Hodgkin disease because they observed no protection of the ovarian reserve with hormonal co-treatment with GnRHa during BEACOPP. Therefore, today there is not enough evidence to apply the GnRHa as a fertility preservation method.

Oophoropexy

Oophoropexy, defined as the action of removing the ovaries surgically from the radiation field, can be offered to oncological patients before initiating treatment with radiotherapy. The procedure can be performed by laparoscopy, because it is simple, safe and effective, unless laparotomy is necessary for the primary treatment of the tumour.[21] Scattered radiation and altered ovarian blood supply appear to be the main factors causing the failure of the technique.[22] The irradiation dose and the total dose received by the less irradiated ovary also affect the result.[23]

When performing oophoropexy, we have to take into account the difficulties of oocyte retrieval in *in vitro* fertilisation (IVF), possible complications in future pregnancies due to uterine irradiation, and ovarian cysts caused by ovarian dysfunction. This technique has shown variable results in the endocrine function recovery (60-90%) according to the treatment used - brachytherapy versus external radiotherapy[24] - and depending on extension, dose and possible vascular involvement. We must not forget the risk of metastasis reported by some researchers when performing this technique in pelvic malignancies, so they advise only recommending this option to those patients with cervical invasive squamous carcinoma without risk factors for ovarian metastases (when there is no vascular invasion) who have to receive radiotherapy.[25] We must wait until we know the real possibilities of this option. Today it is still considered an experimental technique for those patients who have to start a treatment with radiotherapy because of its variable results.[23]

Trachelectomy

Surgical removal of the uterine cervix, called trachelectomy, can be offered to those patients who are affected by a cervical malignancy. In 1994, Daniel Dargent described trachelectomy for the first time, and in 2000 he presented the first results in combination with pelvic

lymphadenectomy.[26] Currently, there are more than 600 published cases of radical trachelectomy with similar survival rates to those with radical hysterectomy. However, we note that their indications are limited to cervical cancer in the early stages.[27] According to ASCO, radical trachelectomy should be restricted to Stage IA2 to IB cervical cancer with diameter <2 cm and invasion <10 mm.[28] The main disadvantages of this technique are posterior infertility problems (usually due to cervical factors), the rate of second trimester miscarriage which is twice that of the general population, and also the higher rate of preterm deliveries.[13]

Embryo Cryopreservation

Embryo cryopreservation, routinely performed in patients undergoing IVF techniques, affords the patient an optimal chance to preserve her fertility, with pregnancy rates of 20-50% per transfer of two to three thawed embryos, depending on the age of the patient at the time her oocyte was retrieved.[29] However, there are some disadvantages to this technique: it cannot be offered to prepubertal patients or adolescents, the patients have to delay their oncologic treatment to carry out the ovarian stimulation (from 2 to 6 weeks, excessive in some cancers), it requires having a partner or accepting a sperm donor, and the supraphysiological levels of gonadotropins and oestradiol resulting from IVF on oestrogen-dependent neoplasms may decrease the usefulness of this treatment for certain patients.[13] Protocols for controlled ovarian hyperstimulation that include agents such as letrozole (aromatase inhibitor) and tamoxifen (selective oestrogen receptor modulator) appear to yield high-quality embryos and counteract the potential impact of high oestradiol levels.[30]

Oocyte Cryopreservation

Oocyte cryopreservation is currently a widely used fertility preservation technique. The oocyte is particularly susceptible to damage during cryopreservation. Recently, vitrification has been shown to give better results in terms of survival, pregnancy and implantation rates than slow freezing.[14]

Cumulative ongoing pregnancy rates with oocyte vitrification without embryo selection in a standard infertility program are comparable to what is obtained with embryo cryopreservation, although female age significantly affects outcomes in this system.[31] The record of Spanish Fertility Society (SEF) in 2010 reports that 12 metaphase II oocytes (MII) are needed to obtain a 59% chance of pregnancy and about 20 MII to reach 80% chance of pregnancy. Further to this, the chance of pregnancy per oocyte thawed (devitrified) is 4-6%. Approximately only one from every five oocytes obtained (20.09%) gives rise to a pregnancy. We must also take into account that the mean number of oocytes obtained in stimulation cycles in the oncology patient is approximately 10.[32] The available evidence indicates that obstetric and perinatal outcomes in infants conceived from vitrified oocytes do not appear to be associated with adverse outcomes.[33]

This technique has similar disadvantages to embryo cryopreservation: it cannot be offered to prepubertal patients or adolescents, the oncologic treatment has to be deferred some weeks and, in hormone-dependent cancers, the ovarian stimulation protocol should be done with letrozole or tamoxifen to avoid the supraphysiological levels of oestradiol. On the other hand, it does not require the patient to have a partner or access to a sperm donor in the moment of the treatment.

Ovarian Tissue Cryopreservation

In prepubertal patients or those patients who require immediate establishment of chemotherapy treatment, the only way to preserve their fertility is cryopreservation of ovarian tissue. The main objective of this strategy is to obtain ovarian tissue for cryopreservation and subsequent thawing and autografting once the patient has recovered from her oncological disease. The ovarian tissue is obtained, as long as possible, by laparoscopy.[34] The standard method of ovarian tissue cryopreservation is slow freezing using propanediol or albumin and dimethyl sulfoxide (DMSO) as cryoprotectants, usually in combination with sucrose,[35] although researchers are working on vitrification protocols to cryopreserve the ovarian tissue. The tissue is cryopreserved in the form of thin cortical strips (about 1-2 mm^3 thickness) to allow penetration of cryoprotectant agents.

Transplantation of ovarian cortical fragments can either be done orthotopically (in the peritoneal cavity or on the contralateral ovary) or heterotopically (forearm or anterior abdominal wall). It is usually performed orthotopically because it allows spontaneous pregnancies. Currently, we know of the existence of 24 newborns from pregnancies achieved in oncological patients who received orthotopic transplantation from their cryopreserved ovarian tissue.[36]

The main problem of this method is the follicular loss, which is due to the cryopreservation procedure and mainly by the ischaemia produced while the graft is revascularised (it is estimated to be responsible for around 60% of the total follicular loss).[14] Currently, the duration of the graft is from 6 to 88 months,[37,38] with a main duration of 4-5 years.[36] In this way, there are some lines of research to accelerate the process of neoangiogenesis, through the use of growth factors combined with the reimplantation of ovarian tissue in a patient with a double oophorectomy.[39] After the transplantation, the assisted reproductive techniques may be used in order to improve chances of pregnancy and these patients should be considered poor responders. On the other hand, another way to improve pregnancy rates is to combine ovarian tissue cryopreservation with embryo or oocyte cryopreservation.

In vitro Maturation

In vitro maturation (IVM) and vitrification of oocytes retrieved from unstimulated ovaries is considered an experimental technique that can be offered to those women that cannot delay their oncological treatment or to adolescents and prepubertal patients. Maturation rates of 79% in oncological patients[40] and clinical pregnancy rates of 18-30% in patients with normal ovulatory cycles have been recorded. Usually multiple embryo transfers are performed because of low implantation rates. On the other hand the high abortion rate is today one of the biggest obstacles to practicing IVM more widely.[41] Currently, IVM must be considered an experimental technique that should not be offered to oncological patients because the experience is still very limited and pregnancy rates are lower than IVF. Huang et al.[40] suggested that IVM can be offered in combination with ovarian tissue cryobanking to increase chances of future pregnancies.

FUTURE TECHNIQUES

More research is still needed to find a procedure that provides the sufficient MII oocytes to ensure a pregnancy that is without risk of reinsertion of malignant cells, without interacting with oncologic treatment, and that provides comparable results to those obtained in healthy women under 35 years of age. In this way, Oktay's theory proposed oocyte regeneration after the case of a 32-year-old patient with a history of Hodgkin's lymphoma was known. The patient underwent ovarian tissue cryopreservation prior to treatment with chemotherapy, radiotherapy and later, bone marrow transplantation. After heterotopic transplantation of ovarian tissue she became pregnant repeatedly in a spontaneous way and three healthy babies were born. According to the author, this could be due to a connection between the ovary and bone marrow. Bone marrow reserve would act as peripheral germline stem cells and non-steroidal factors required for the differentiation of germ cells would come from the ovarian tissue.[42,43]

Another interesting theory is one which deals with the maturation of primordial follicles in ovarian tissue fragments. So we have a significant reserve of primordial follicles and IVM would allow us to obtain MII oocytes. After the initial work of Picton et al.[44] on IVM from primordial follicle to the MII oocyte, Krotz et al.[45] proposed the artificial ovary. They used the three-dimensional cultures, achieving maturation from early antral follicles (under 10 mm) to MII oocytes. They achieved interaction, growth and functionalism of the ovarian three cell lines: oocytes, granulosa and theca. These options are only two theories and, currently, these must not be taken as options for fertility preservation as studies in these fields need to be furthered.

CONCLUSION

Recent advances in oncological treatment and early diagnosis of cancer diseases have led to an increase in the survival rates of cancer patients. Due to this, more and more women suffer side-effects of oncological therapies such as premature ovarian failure. Clinicians must ensure that these women are referred to fertility specialists to obtain the best advice in fertility

preservation techniques. Embryo and oocyte cryopreservation are well-established techniques that can be useful in adult women who are able to delay their oncologic treatment by a few weeks. Ovarian cryopreservation is an experimental procedure, and the only one that can be offered to prepubertal patients or to those patients who have to start the oncological therapy immediately. The characteristics of the patient must always be assessed and each case individualised to advise the best fertility preservation option. Finally, we must not forget that we can recommend a combination of techniques to optimise fertility options.

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Autism testing of the foetus

AUTISM could be addressed in the foetus by testing the umbilical cord blood levels for growth protein. Dr Gary Steinman, Chairman of the Department of Biochemistry, Touro College of Osteopathic Medicine, New York, USA, has suggested that the role of depressed insulin-like growth factor (IGF) may be a biomarker which could anticipate autism occurrence.

Dr Steinman said: "By assessing our own research, along with dozens of other relevant studies, there is a strong case to be made that IGF – known to be deeply involved in the normal growth and development of babies' brain cells – also serves as a biomarker for autism."

In brain biopsies of autistic individuals there is evidence of insufficient IGF. This in turn results in insufficient insulating material, called myelin, which helps to efficiently transmit important messages of all that the brain controls, from physical to mental functions. This insufficiency may impede proper pathway development.

Dr Steinman has suggested that a sample of umbilical cord blood should be collected immediately after birth to measure IGF. The data collected at birth would then be compared with a neurologic evaluation of the baby at 18-36 months. If the levels of IGF were low then the baby could receive a supplemental amount of protein by breastfeeding. An increase in the duration of breastfeeding can be associated with a decreased incidence of autism.

If more research is conducted confirming the connection between IGF and autism, a new phase of research focusing on the detection of depressed levels of IGF in the second trimester of pregnancy, can come to the forefront.

Dr Steinman said: "These findings send a powerful message to the research community. Our research is consistently indicating a connection between IGF and autism. The medical community needs to vigorously investigate this ostensible connection and validate it once and for all."

Dr Steinman added: "As we all know full well, the world would reap untold benefits by finding ways to detect, treat and ultimately prevent this disease."

"Our research is consistently indicating a connection between IGF and autism. The medical community needs to vigorously investigate this ostensible connection and validate it once and for all."

Dr Gary Steinman
Touro College of Osteopathic Medicine, New York, USA

The impact of asthma on fertility

ASTHMA could impact a woman's fertility rate by causing difficulty in conceiving, and as a result, they can experience a prolonged time to pregnancy.

Data were collected from a cohort study, which included 15,000 participants, with an average age of 27. The participants were then divided into two groups – asthma and non-asthma. In the asthma group, 27% of women experienced prolonged time to pregnancy while only 21.6% of women in the non-asthma group experienced this problem.

The women were also divided into sub-groups – those treated for asthma, and those not treated. The results showed that in the untreated group, 30.5% had an increased delay in conception, whereas in the other group, 23.8% experienced this problem.

"Although we observed women with asthma experiencing longer waiting times to pregnancy, our findings suggest that if women take their medication and control their asthma, they can reduce this delay."

Dr Elisabeth Juul Gade
Bispebjerg University Hospital, Denmark

Furthermore, the researchers discovered that age was also a factor. Compared to their non-asthmatic counter-parts, women over the age of 30 with asthma, had a 32.3% longer waiting time to pregnancy, compared to women with asthma under the age of 30, who only had a rate of 24.9%.

Lead author, Dr Elisabeth Juul Gade, Bispebjerg University Hospital, Denmark, said: "Our results shed light on the complex interactions between fertility and asthma. Although we observed women with asthma experiencing longer waiting times to pregnancy, our findings suggest that if women take their medication and control their asthma, they can reduce this delay.

"Despite the delay," Dr Gade adds: "Our overall results suggest that women with asthma had the same number of children, which is due to the fact that they tend to conceive at an earlier age compared to those without, getting a head start on their reproductive life."

PROMISING DATA FOR PREGNANT WOMEN FOLLOWING C-SECTION

"This study shows encouraging results with the majority of women who attempted a natural delivery after a primary C-section being successful."

Mr John Thorp
Deputy Editor-In-Chief,
BJOG: An International Journal of Obstetrics and Gynaecology

A NEW study indicates that of the women who attempted a vaginal birth after caesarean section (VBAC), around two-thirds of these were successful.

Factors determining the uptake and success rate of natural birth after caesarean sections (C-sections) were investigated by the Office for Research and Clinical Audit (ORCA) at the Royal College of Obstetricians and Gynaecologists and the London School of Hygiene and Tropical Medicine, UK.

Data were analysed between 2004 and 2011; of the 143,970 women considered, they discovered 52% attempted a VBAC for their second child. Of these women, almost two-thirds (63%) were successful, and women aged over 34 had a lower success rate compared to women of 24 years or younger.

Researchers established that factors attributing to the first C-section strongly influenced the probability of a successful natural delivery in the next pregnancy.

Lead researcher, Hannah Knight, Office for Research and Clinical Audit, Royal College of Obstetricians and Gynaecologists, stated: "The majority of women with an uncomplicated first caesarean section are candidates for attempting VBAC, but our data found that only half of those women chose this option."

She added: "Interestingly, we also found an unexplained variation in the rate of attempted and successful VBAC between hospitals, which was independent of maternal demographic and clinical risk factors."

Mr John Thorp, Deputy Editor-In-Chief, BJOG: An International Journal of Obstetrics and Gynaecology, mentioned: "In England approximately 50,000 women per year are faced with the choice of attempting a trial of labour after having had a C-section for their first delivery. This study shows encouraging results with the majority of women who attempted a natural delivery after a primary C-section being successful."

PARP inhibitors: Leading the way for endometrial cancer

OESTROGEN levels can improve the effect of poly ADP-ribose polymerase (PARP) inhibitors in endometrial cancer, also known as, womb cancer.

The aim of the researchers, from the University of California, Los Angeles (UCLA), USA, was to evaluate whether PARP inhibitors would be effective in a laboratory model within a tumour microenvironment which would resemble human endometrial cancer.

In the USA, the National Cancer Institute have estimated that 49,560 new cases of endometrial cancer will be reported in 2013, and approximately 8,190 deaths are expected to occur. In 80% of endometrial cancers there is an absence of a protein, phosphatase and tensin homolog (PTEN), which is a tumour suppressor.

> "In our experiments, we found that tumours treated with the inhibitors did show decreased growth, but that this did not rely solely on the loss of PTEN."
>
> *Dr Daniel Paik*
> *Study Investigator, UCLA, USA*

Dr Daniel Paik, an investigator in the study, said: "In our experiments, we found that tumours treated with the inhibitors did show decreased growth, but that this did not rely solely on the loss of PTEN."

In a low oestrogen environment, there was a significant reduction in tumour size; as there was a higher amount of drug detected within the bloodstream, more PARP inhibitors were available to fight the cancer.

> "This study showed us that endometrial cancers that have defects in PTEN are sensitive to PARP inhibition, but the response hinges on low levels of oestrogen."
>
> *Dr Sanaz Memarzadah*
> *Assistant Prof, Obstetrics and Gynaecology, UCLA, USA*

Surprisingly, in a high oestrogen environment there was no response to the PARP inhibitors. The tumours repaired cell damage, and in turn, the built-up DNA repair meant that there was resistance to the PARP inhibitor, this was contrary to what was seen in a low oestrogen environment.

"This study showed us that endometrial cancers that have defects in PTEN are sensitive to PARP inhibition, but the response hinges on low levels of oestrogen," said Dr Sanaz Memarzadah, Assistant Prof of Obstetrics and Gynecology, UCLA. He added: "The difference in the response was remarkable. It was like night and day."

The results of these findings may mean that personalised therapy in women with advanced endometrial cancer can be developed, and alternative treatment options which will have more efficacy could be produced. Moreover, these findings could be relevant to other hormone-driven cancers, such as breast, ovarian, and prostate cancer.

Fertility breakthrough: Infertile women treated with *in vitro* activation

INDUCTION of the ovaries can bring hope to infertile women to enable them to start producing eggs. This technique called '*in vitro* activation' (IVA) resulted in the birth of a healthy baby.

IVA involves the removal of the ovary, or part of it, which is then treated and re-implanted within the vicinity of the fallopian tubes. The patient is treated with hormones to stimulate the growth of follicles. IVA has been the work of researchers from Stanford University School of Medicine, USA, and the clinical collaborators from St. Marianna University School of Medicine, Kawasaki, Japan, utilised this technique in an experimental study involving women suffering from primary ovarian insufficiency.

Prof Aaron Hsueh, Professor of Obstetrics and Gynecology, Stanford University School of Medicine, USA, and senior author said: "Women with primary ovarian insufficiency enter menopause quite early in life, before they turn 40."

Prof Hsueh added: "Previous research has suggested that these women still have very tiny, primordial and secondary follicles, and that even though they are no longer having menstrual cycles they may still be treatable."

The study involved 27 women in whom both ovaries were removed via minimally invasive procedures. The average age of participants was 37 years and participants had stopped menstruating on average 6.8 years prior to the operation. Of the 27 participants, 13 women had contained residual follicles. From this proportion, eight of the women had follicle growth and were then treated with hormones to stimulate ovulation. Only five women had developed matured eggs which were then fertilised *in vitro* with their partners' sperm. The four-cell embryos were frozen and transferred into the uterus.

One woman progressed onto a normal pregnancy and gave birth to a healthy baby and another is currently pregnant.

"Previous research has suggested that these women still have very tiny, primordial and secondary follicles, and that even though they are no longer having menstrual cycles they may still be treatable."

Prof Aaron Hsueh
Stanford University School of Medicine, USA

Preventing cervical cancer with just one HPV vaccination

PREVENTION against cervical cancer may be possible with just a single dose of the human papillomavirus (HPV) vaccine.

"Our findings suggest promise for simplified vaccine administration schedules that might be cheaper, simpler, and more likely to be implemented around the world," said Dr Mahboobeh Safaeian, Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA.

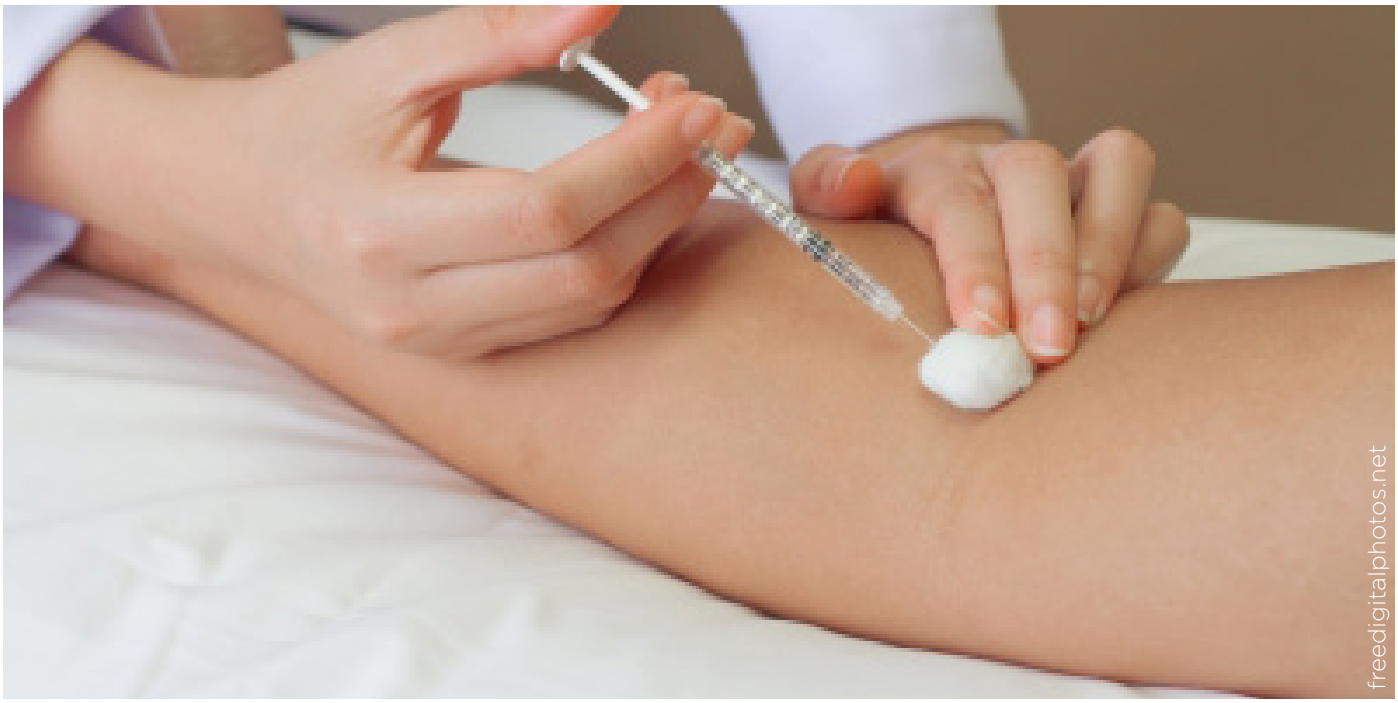
Present guidelines recommend that the vaccines, Gardasil or Cervarix, should be administered three times in girls aged 11 or 12, or for girls aged 13 to 26 who have not yet been vaccinated.

The vaccine coverage between 2006 and 2013 was 53.8% of girls aged between 13 and 17, of these, only 33.4% had all three doses.

Using data from a Phase III trial funded by the National Cancer Institute (NCI), researchers found that around 20% of the girls included in the Phase III study had not received the full three doses of the HPV vaccine. The researchers analysed the antibody levels in the blood samples drawn from 78 women who received one vaccination, 192 women who received two vaccinations, and 120 women who received three doses.

100% of women in all three groups had antibodies against HPV 16 and 18 in their blood for 4 years. Although the antibody levels in the women who received one dose were lower than among those who received the full three doses, their levels appeared stable, suggesting that there was a lasting response.

Although these findings are encouraging, more research needs to be conducted so that the guidelines can be changed.



Ethnicity influencing positive pregnancy outcomes

"Further research into genetic background as a potential determinant of IVF outcome, as well as the influencing effects of lifestyle and cultural factors on reproductive outcomes, is needed."

Dr Walid Maalouf
University of Nottingham, UK.

ETHNICITY of the mother can have an impact on the successful outcomes after fertility treatment. More research is needed in order to understand how ethnicity can be an indicator for successful treatment.

Researchers from the University of Nottingham, UK, gathered data between 2006 and 2011. They studied 1,517 women, 85.1% were of white European descent, and the remaining 14.9% were from ethnic minority groups. Both groups were undergoing their first cycle of fertility treatment, which included *in-vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

The results showed that 43.8% of white European women gave birth to a live baby, compared with only 35% of ethnic women. In clinical pregnancy rates, 47.9% of white European women were successful compared to 38.5% of ethnic women. For implantation rates, 37.4% of white European women were successful, while only 22.6% of ethnic women were successful.

Lead researcher of the paper, Dr Walid Maalouf, from NURTURE, Division of Child Heath, Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences University of Nottingham, said: "Our data indicates that live birth rates, clinical pregnancy rates and implantation rates following fertility treatment, particularly IVF, are significantly lower in ethnic women when compared to white Europeans.

"The reason for the reduced implantation rates and subsequent reduced outcomes in the ethnic minority group is still unclear. Further research into genetic background as a potential determinant of IVF outcome, as well as the influencing effects of lifestyle and cultural factors on reproductive outcomes, is needed."

The results of this study will enable healthcare professionals to counsel couples about their realistic probabilities of a positive outcome after fertility treatment. This research could also encourage women from ethnic backgrounds to seek treatment earlier, which in turn, could improve their chances of a positive pregnancy outcome.

Unmasking reasons for infertility

NANOPARTICLES are being investigated by researchers at Oxford University, UK, to discover the underlying mechanisms causing instances of unknown infertility.

The method includes loading porous silica nanoparticle pockets with compounds which will help to identify and diagnose the causes of infertility, and then possibly treat these causes.

> "An attractive feature of nanoparticles is that they are like an empty envelope that can be loaded with a variety of compounds and inserted into cells."
>
> *Dr Natalia Barkalina*
> *Oxford University, UK*

Dr Natalia Barkalina, lead author of the study from the Nuffield Department of Obstetrics and Gynaecology at Oxford University, stated: "An attractive feature of nanoparticles is that they are like an empty envelope that can be loaded with a variety of compounds and inserted into cells." She continued: "The nanoparticles we use don't appear to interfere with the sperm, making them a perfect delivery vessel."

Sperm is a vital element of fertility research, however, they are difficult to examine due to their unusual shape, small size, and short lifespan outside of the body. Dr Kevin Coward, senior author, Nuffield Department of Obstetrics and Gynaecology at Oxford University, explained how concentrating on sperm to see where the problems begin is important, and this new approach will accelerate, and simplify the procedures,

as sperm can be exposed to the nanoparticles in a petri dish. The sperm is able to survive due to the quickness of the process. In their trial, boar sperm was used due to its similar composition to human sperm.

Co-author, Celine Jones, from the Institute of Reproductive Sciences, Oxford, stated: "It is similar in size, shape and activity. Now that we have proven the system in boar sperm, we hope to replicate our findings in human sperm and eventually see if we can use them to deliver compounds to eggs as well."

Are steroid levels the missing link for recurrent miscarriages?

STEROID levels may be the answer for women who have suffered from recurrent miscarriages.

More than one in seven pregnancies end in miscarriage. Recurrent miscarriages, losing three or more pregnancies in a row, affects one in 100 women in the UK.

Prof Siobhan Quenby, University of Warwick, UK, said: "It causes incredible psychological distress and anguish. The routine advice in the UK is if blood tests identify no cause then there's no treatment, that's terribly unacceptable to patients."

The researchers believe that the level of 'natural killer' NK cells are a marker of something more serious occurring in the lining of the womb. The researchers have found that low steroid levels make the womb lining less likely to accept an embryo, and damage the way it nourishes a foetus. This process leads to steroid deficiency which, in turn, was an indicator of high NK cell levels.

There are now demands for clinical trials which will decide whether steroids are able to help women to become pregnant. Patients are advised not to go and buy steroids as surplus may also lead to a miscarriage, and it may do more harm.

Prof Nick Macklon, Prof of Gynaecology and Obstetrics, University of Southampton, UK, said: "This is a crucial breakthrough in the understanding of recurrent miscarriage, it's the gateway to the clinical trial.

"But what this shows is that steroids shouldn't be given to all, we need to be sure that is the problem in women before they're given."

The effect of obesity on female puberty

OBESITY is playing a part in girls experiencing puberty earlier. This early change can lead to lower self-esteem, hypertension, and also several cancers, including breast, ovarian, and endometrial cancer.

Dr Frank Biro, lead investigator, Physician at Cincinnati Children's Hospital Medical Center, USA, said: "The current study suggests clinicians may need to redefine the ages of both early and late maturation in girls."

Studying 1,239 girls aged 6-8 years of age from 2004-2011, the researchers examined the age at which breast development began and the impact it had on body mass index (BMI), as well as factoring in race/ethnicity. Researchers found that the median age for breast development for African-Americans was 8.8 years of age, 9.3 for Hispanic girls, 9.7 for Caucasian girls (this age is earlier than what has been previously reported), and 9.7 for Asian girls.

BMI served as an even stronger link for earlier onset of puberty. Their results indicated that there was a correlation between higher BMI and earlier breast maturation. Overweight and obese girls developed breasts around the age of 8, compared to normal weight girls who developed breasts around the age of 9.

"This impact of earlier maturation in girls has important clinical implications involving psychosocial and biologic outcomes," said Dr Biro.

It has been suggested by the team that the earlier start to puberty in Caucasian girls is likely due to greater obesity. The team is conducting further research to identify specific environmental and physiological factors behind this trend.

Cholesterol: The new driving force of breast cancer

CHOLESTEROL metabolite, 27-hydroxycholestrol (27HC), promotes cancer growth in oestrogen-receptor positive breast cancers.

Dr Philip Shaul, Professor and Vice Chair for research in Paediatrics and member of the Harold C. Simmons Comprehensive Cancer Center, USA, said: "This information can be used to develop new therapies that inhibit 27HC action or production, or increase its metabolism, in effect cutting the cancer off from a key growth stimulator."

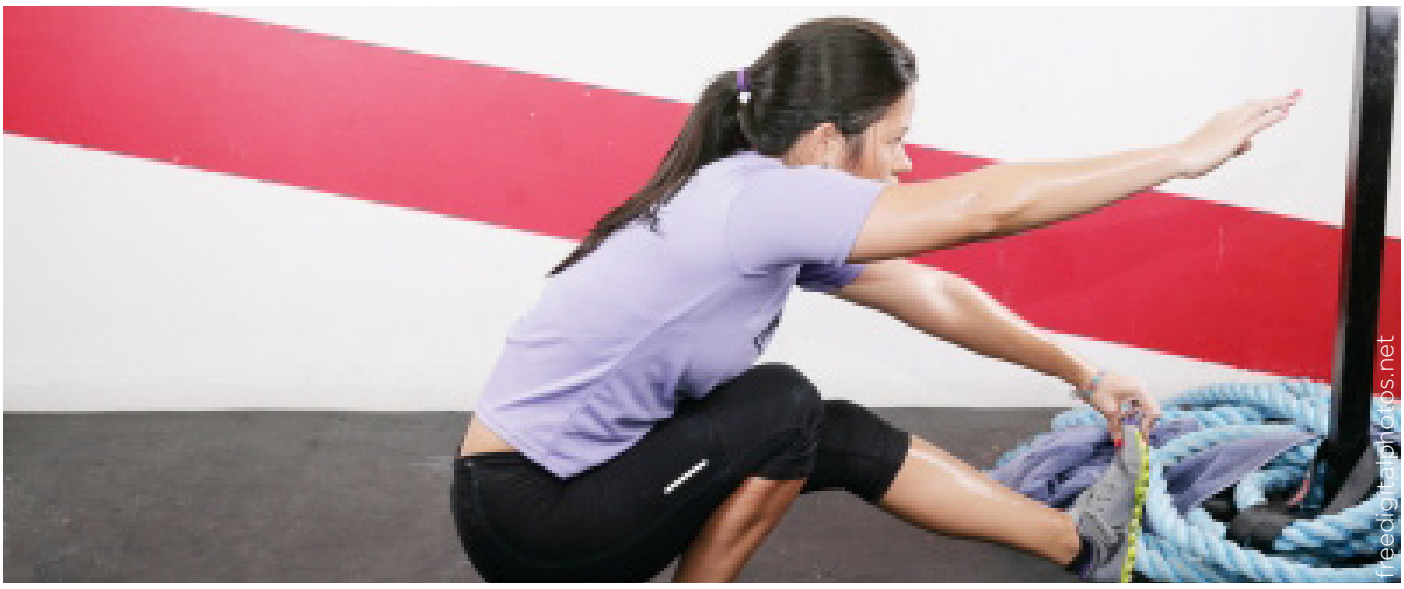
The research team discovered that 27HC stimulates the growth of breast cancer cells by hijacking growth-promoting mechanisms triggered by the oestrogen receptor.

It was observed that in breast cancer patients, there was a higher concentration of 27HC in breast tissue in comparison to cancer-free controls. The research team focused their research on past investigations in cholesterol metabolism, where the enzyme CYP7B1 was discovered to metabolise 27HC. It was observed that the concentration of CYP7B1 was significantly reduced in breast tumours when compared with normal breast tissue. There was a 7-fold poorer survival rate with tumours displaying low CYP7B1, in comparison to tumours with high CYP7B1.

"Measurements of tumour CYP7B1 or 27HC content could provide a potentially critical new means to personalise endocrine-based therapy for women with breast cancer," said Dr Shaul. "Ultimately, the translation of these new findings to the clinical setting may also involve determinations of tumour CYP7B1 or 27HC abundance to serve as prognostic indicators."

"This information can be used to develop new therapies that inhibit 27HC action or production, or increase its metabolism, in effect cutting the cancer off from a key growth stimulator."

Dr Philip Shaul
Harold C. Simmons Comprehensive Cancer Center, USA



Link between sex hormones and cognition in menopausal women

SEX hormones have been linked to changes in cognitive ability and mood in menopausal women.

Researchers investigated the relationship between sex hormones and cognition in postmenopausal women (both young and old). Age, and the time elapsed since they reached menopause, were the main parameters taken into account for the study.

Data from 643 healthy postmenopausal women, with the age range of 41-84 were analysed, none of whom were undergoing hormone therapy. They were divided into two groups: those that experienced menopause less than 6 years before, and those who experienced menopause more than 10 years ago. The participants undertook a series of neuropsychological tests to test memory and cognition. Their levels of oestradiol, oestrone, progesterone, and testosterone were measured, they were also assessed for depression.

Researchers from Stanford University School of Medicine, USA, have speculated: "Some effects might be more beneficial for younger postmenopausal women closer to the time of menopause than for older postmenopausal women."

The research team hypothesised that increased levels of oestradiol could increase memory performance in younger menopausal women more than older menopausal women.

"Instead, we found no significant link – positive or negative – in either group," said Dr Victor Henderson, lead author and Professor of Health Research and Policy and of Neurology and Neurological Sciences, Stanford University School of Medicine.

Dr Henderson added that the findings do not "necessarily mean that oestrogens are irrelevant to cognition, since we have no way of measuring oestrogen directly at the brain level. But they imply that boosting blood levels of oestradiol or oestrone – even in younger postmenopausal women – may not have a substantial effect on cognitive skills one way or the other."

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Basic Practical Skills in Obstetrics and Gynaecology

9th–11th Jan 2014

Belfast, Ireland

Held in a structured workshop environment, trainees will be introduced to safe surgical techniques and obstetric clinical skills. The course will complement the Royal College of Obstetricians and Gynaecologists Training Portfolio Logbook, and is linked to OSATS.

2014 Progress and Controversies in Gynecologic Oncology Conference

24th–25th Jan 2014

Barcelona, Spain

This meeting will present and discuss new data available across various gynecologic malignancies, including ovarian cancer, cervical, and endometrial cancers. Updates on practice-changing data and impacting clinical outcomes for patients will be discussed in an interactive format.

Maternal Medicine: Medical Complications in Pregnancy

5th–6th Mar 2014

London, UK

This event, which attracts a wide range of internationally renowned speakers, is tailored towards trainees, consultants, and midwives. Throughout the conference, current maternal medicine issues across all medical subspecialties with specific relevance to obstetrics will be addressed in a series of lectures and breakout groups.

16th World Congress of Gynecological Endocrinology

5th–8th Mar 2014

Florence, Italy

One of the major events in developing, upgrading, and teaching gynecological endocrinology. The Congress will consist of plenary lectures, debates, and sessions, each of which will include up to five speakers presenting their scientific research. There will also be a number of symposia held by scientific societies.

Early Pregnancy and Emergency Gynaecology

19th–20th Mar 2014

London, UK

All healthcare professionals with an interest in early pregnancy and acute gynecology are urged to attend. This event hopes to update consultants and trainees regarding recent developments in clinical practice within this specific branch of medical treatment.

XII Annual Meeting of the Mediterranean Society for Reproductive Medicine (MSRM) and COGI-BCGIP

24th–26th April 2014

Barcelona, Spain

MSRM and COGI have joined forces to promote excellence in the field, and aims to bridge the gaps between the expansion of information and the implementation in clinical practice. International and local experts will share experiences in many stimulating debates, sessions, and speaker-audience discussions. Even when proof is lacking in ongoing debates, the Congress aims to reach up-to-date and agreed upon answers through the use of evidence-based medicine and expert opinion.

23rd European Congress of Obstetrics and Gynaecology

7th–10th May 2014

Glasgow, Scotland

Throughout this Congress there will be hands-on training, courses, and a social programme which will give attendees a chance to meet colleagues. The scientific programme will focus on a number of topics, including reproductive medicine, IVF in woman with cancer, breast cancer, treatment and prevention of gynecological cancers, and many other topics.

13th ESC Congress 'Challenges in Sexual and Reproductive Health'

28th–31st May 2014

Lisbon, Portugal

To contribute to this year's theme there will be a number of presentations and discussions, all of which will focus on the latest scientific information and knowledge regarding contraception, as well as promoting every individual's right to access adequate health services and to be informed on methods of family planning.


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