UNIVERSIDADE D
COIMBRA

Ana Beatriz Precatado da Silva

Relatório de Estágio e Monografia intitulada "Endocrine disruptors present in food and their role in female infertility" referente à Unidade Curricular "Estágio" sob orientação, da Dra. Sónia Marisa Ponte Costa e da Professora Doutora Ana Teresa Sanches Silva e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas

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Julho 2021

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Coimbra, 2 de julho de 2021.

Ana Beatriz Precatado da Silva

(Ana Beatriz Precatado da Silva)

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À Lita.

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RELATÓRIO DE ESTÁGIO EM FARMÁCIA COMUNITÁRIA

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FARMÁCIA DO FORUM

Orientado pela Dra. Sónia Marisa Ponte Costa

Lista de Abreviaturas

DCI - Denominação Comum Internacional

FF - Farmácia do Forum

MICF - Mestrado Integrado em Ciências Farmacêuticas

MNSRM - Medicamentos não sujeitos a receita médica

MSRM - Medicamentos sujeitos a receita médica

PVP - Preço de venda ao público

SWOT - *Strengths, Weakness, Opportunities* and *Threats*

1. Introdução

Os farmacêuticos comunitários, enquanto consultores de saúde de confiança, devem promover o uso seguro e correto de medicamentos assim como melhorar os resultados clínicos da população.

Desde 1449 que existem farmacêuticos em Portugal, conhecidos na altura como boticários, onde as suas funções passavam maioritariamente pela preparação oficial de medicamentos. Com o passar do tempo, foi havendo uma evolução nesta atividade, passando a centrar-se fundamentalmente no serviço à comunidade, dando origem à designação atual de farmácia comunitária.[1]

Um farmacêutico comunitário, enquanto agente de saúde, detém inúmeras funções, e é seu o dever de disponibilizar ao cidadão em geral, um tratamento com qualidade, eficácia e segurança. Daqui advém a extrema importância do seu papel enquanto profissional de saúde sendo da sua responsabilidade muitas das tarefas que pertencem aos medicamentos.[2]

Ao longo do meu percurso académico, fui intensivamente formada em diferentes unidades curriculares, que me deram competências essenciais para responder assertivamente aos muitos desafios que me foram colocados enquanto estagiária na área de farmácia comunitária. Para além dos conhecimentos académicos adquiridos, foi igualmente enriquecedor, a aprendizagem que fiz com os meus colegas de trabalho, que me guiaram, corrigiram e esclareceram as dúvidas que foram surgindo.

O relatório aqui presente, serve para retratar o estágio curricular em farmácia comunitária que tive o privilégio de vivenciar. Este, teve início a 7 de setembro e posterior conclusão a 3 de fevereiro de 2021, com uma duração total de 810 horas, na Farmácia do Forum (FF) em Coimbra, sob a orientação da Dra. Sónia Costa.

O subsequente relatório encontra-se na forma de análise SWOT, tal como referido nas "Normas Orientadoras de Estágio do Mestrado Integrado em Ciências Farmacêuticas".[3] Trata-se de um método de análise dividido em quatro pontos: "*Strengths, Weakness, Opportunities* and *Threats*".

2. Análise SWOT

Dimensão Interna	
Pontos Fortes (*Strenghts*)	**Pontos Fracos (*Weaknesses*)**
Localização da farmácia e horário de funcionamento alargado. Excelente acompanhamento e ambiente de trabalho. Inovação tecnológica. Autonomia e responsabilidade. Integração de conhecimentos teóricos.	Sazonalidade do Estágio. Dificuldade na associação nome comercial – Denominação Comum Internacional (DCI).
Dimensão Externa	
Oportunidades (*Opportunities*)	**Ameaças (*Threats*)**
Participação em formações internas. Participação em campanhas de *marketing*.	Medicamentos esgotados. Espaços de venda de MNSRM. COVID-19. Tentativa de compra de MSRM sem receita médica.

A análise SWOT é uma técnica de planeamento estratégico, que desmontando o acrónimo que a constitui, surgem os quatro pontos que a constituem: "*Strengths, Weakness, Opportunities* and *Threats*" que traduzindo, dá origem a Pontos Fortes, Pontos Fracos, Oportunidades e Ameaças.

Deste modo é feita uma análise bem estruturada e objetiva, dividida em duas grandes dimensões: a dimensão interna (pontos fracos e fortes), que diz respeito aos fatores intrínsecos do estágio para a minha formação, e a dimensão externa (ameaças e oportunidades) referentes por sua vez, aos fatores extrínsecos desta etapa.[4]

2.1 Pontos Fortes (*Strenghts*)

2.1.1 Localização da Farmácia e Horário de Funcionamento Alargado

A Farmácia do Forum, encontra-se instalada no centro comercial Forum Coimbra, que por sua vez se encontra no planalto Santa Clara. É o maior centro comercial da cidade de Coimbra, caracterizado pelo grande fluxo de movimento, tanto da população pertencente ao centro da cidade, como da população que reside nas áreas periféricas da mesma, o que contribui para o grande fluxo de clientes, que caracteriza esta farmácia, a par do horário alargado (de segunda feira a domingo das 9:00 às 00:00).[5]

A Farmácia do Forum tanto funciona como uma farmácia de passagem, para os clientes ocasionais que vão ao centro comercial por razões diversas, e acabam por ser relembrados de alguma necessidade referente à farmácia, e essencialmente, como uma farmácia local, para todos os clientes habituais e fidelizados, que por razões de aproximação do seu local de residência, ou confiança no serviço prestado pela mesma, acabam por aceder sempre a esta farmácia como serviço de preferência.

A Farmácia do Forum funciona como farmácia local, para todos os clientes habituais e fidelizados, que por razões de aproximação do seu local de residência, ou confiança no serviço prestado pela mesma, acabam por aceder sempre a esta farmácia como serviço de preferência, mas também como uma farmácia de passagem, para os clientes ocasionais que vão ao centro comercial por razões diversas, e acabam por ser relembrados de alguma necessidade referente à mesma.

Neste contexto tive a oportunidade de contactar com uma vasta variedade de utentes e problemas dissemelhantes que contribuíram para o meu enriquecimento, tanto pessoal como profissional.

2.1.2 Excelente acompanhamento e ambiente de trabalho

Um dos pontos cruciais para uma empresa ter sucesso e prosperar é sem dúvida o ambiente de trabalho que se vive diariamente entre equipa. Este é um ponto com o qual saio muito satisfeita deste estágio, tendo-se verificado um ambiente muito agradável, dinâmico e pedagogicamente fortalecedor.

Foi-me apresentado um plano, no início do estágio, pelo qual me fui guiando durante os meses de estágio, de forma a conseguir inteirar-me por completo das diferentes funções que cada profissional ali presente detém e da sua importância no bom funcionamento da empresa. Tive oportunidade de observar e executar as mais diversas tarefas, sempre acompanhada pela minha orientadora e os restantes colegas, que me foram esclarecendo e guiando, promovendo a minha crescente autonomia.

A disponibilidade que me foi presenteada, por todos os membros da equipa, na explicação e esclarecimento de todas as etapas, esclarecendo-me as dúvidas que foram surgindo, foi determinante para o sucesso do mesmo.

2.1.3 Inovação tecnológica

Atualmente, o acompanhamento das empresas no crescimento tecnológico, é crucial para distinguir um bom estabelecimento. A Farmácia do Forum, revela valorizar as tecnologias ao serviço da farmácia, dispondo de um *robot*, com alta capacidade de armazenamento, onde a grande parte do atendimento recai. O *robot* é um investimento com alto retorno, diminuindo consideravelmente o tempo despendido na arrumação dos medicamentos, atividade que tem de ser feita muito mais que uma vez ao dia, e em toda a verificação mensal das validades das embalagens lá armazenadas. Para além disso, promove a redução do tempo médio de atendimento, uma vez que o tempo de procura da embalagem certa é retirado da equação, tornando os clientes mais satisfeitos com a eficácia e a prontidão com que são atendidos.

A farmácia também utiliza um "*CashGuard*" de forma a organizar a sua caixa. O "*CashGuard*" permite não só a redução do tempo de atendimento, mas também evita os erros nos trocos, o que resulta numa diminuição nas incoerências na caixa ao final do dia.

2.1.4 Autonomia e Responsabilidade

Desde cedo que me foi dada autonomia em todas as tarefas que me eram entregues. Considero a autonomia uma ferramenta essencial para quem ambiciona tornar-se cada vez melhor no que exerce. Assim, encarei o estágio com um sentido de responsabilidade acrescido, sempre trabalhando o mais atenta possível, tentando diminuir ao máximo as minhas falhas, de modo a não penalizar a farmácia nem o utente. Foi-me permitido crescer de uma maneira gradual, e cada vez mais autónoma, o que me tornou numa estagiária com confiança, onde as inseguranças foram metamorfoseadas em forças.

Tudo isto, fez com que eu conseguisse experienciar verdadeiramente o peso que esta profissão acarreta e, juntamente, sentir, pela primeira vez, o conceito de identidade profissional.

2.1.5 Preparação de Manipulados

Na Farmácia do Forum reúnem-se as condições necessárias para a preparação de manipulados prevista pela Portaria n.º 594/2004, onde estão assentes "oito vertentes essenciais, a saber: pessoal, instalações e equipamentos, documentação, matérias-primas, materiais de embalagem, manipulação, controlo de qualidade e rotulagem".[6]

Esta prática surge como forma a colmatar possíveis lacunas no mercado, que apesar de cada vez mais abrangente e inclusivo, ainda existe necessidade de manipulação de medicamentos, de forma a adaptar a terapêutica medicamentosa a um determinado utente.

Tal como previsto no Decreto-Lei n.º 95/2004, a preparação de medicamentos manipulados, deverá recair aquando das seguintes situações:

> "3 - O descondicionamento de especialidades farmacêuticas, com a finalidade de as incorporar em medicamentos manipulados, é um acto de excepção, só podendo realizar-se se não existir no mercado especialidade farmacêutica com igual dosagem ou apresentada sob a forma farmacêutica pretendida e apenas nos seguintes casos:
>
> a) Medicamentos manipulados destinados a aplicação cutânea;
>
> b) Medicamentos manipulados preparados com vista à adequação de uma dose destinada a uso pediátrico;
>
> c) Medicamentos manipulados destinados a grupos de doentes em que as condições de administração ou de farmacocinética se encontrem alteradas."[7]

Durante o estágio tive a oportunidade de assistir a diversas preparações de manipulados, inclusive o privilégio de realizar autonomamente um. O manipulado que preparei denomina-se como "suspensão oral de enalapril 1mg/mL", e trata-se de um caso destinado a uso pediátrico, que urge da necessidade de adequação da dose.

Com o objetivo de melhorar o serviço e de providenciar um apoio técnico-científico, o LEF disponibiliza às farmácias o Centro de Informação de Medicamentos de Preparação Individualizada (CIMPI).[8]

Posto isto, e seguindo um dos protocolos estabelecidos pelo LEF, foi preparada uma "suspensão oral de enalapril 1mg/mL". O veículo utilizado, ao contrário do previsto pelo Formulário Galénico Português, foi o "SyrSpend® PH4", que apresenta uma estabilidade muito superior (90 dias) comparado ao xarope comum.[9] Para além desta clara vantagem, surge também outro ponto a favor na utilização deste veículo, o "SyrSpend® PH4" escolhido para este caso, é caracterizado por dispor de um sabor a cereja. Esta é uma escolha que eu considerei muito interessante, principalmente quando se trata de população pediátrica, onde por vezes a toma da medicação, se torna um desafio para os pais e/ou cuidadores, devido à rejeição que ocorre em resposta a sabores, por vezes desagradáveis, de algumas formulações.

Durante a preparação do manipulado, pude aplicar várias técnicas laboratoriais aprendidas ao longo do curso, o que facilitou todo o processo.

Após a preparação, segundo o procedimento descrito na Farmacopeia Portuguesa, procede-se ao preenchimento da "Ficha de Preparação de Medicamentos Manipulados", onde

se encontram descritas todas as informações relativas à mesma (Anexo 1). Esta ficha, após preenchimento, é datada e assinada tanto pelo operador como pelo supervisor, e é arquivada juntamente com uma cópia da receita e do respetivo rótulo (Anexo 2).

2.1.6 Integração de conhecimentos teóricos

Este estágio corresponde ao último passo do curso de Mestrado Integrado em Ciências Farmacêuticas (MICF), onde conhecimentos foram adquiridos e assimilados ao longo deste percurso de 5 anos. Foram muitas as unidades curriculares que me permitiram executar este estágio de uma forma não tão primígena e já sim com algum conhecimento prévio.

Em muitas ocasiões tive de recordar e utilizar os conhecimentos obtidos, por exemplo, quando num atendimento somos abordados por uma opinião, que necessita de uma base científica para ser respondida convenientemente, ou por uma questão acerca das possíveis interações medicamentosas, a nível da indicação terapêutica em casos resolvíveis na farmácia onde não há receita médica, interpretação de valores e parâmetros bioquímicos para praticar um aconselhamento informado, entre outros.

Com isto, sinto que o plano de estudos do MICF foi crucial e bem estruturado, de maneira a que este estágio possa ser realizado de uma forma mais natural e consciente.

2.2 Pontos Fracos (*Weaknesses*)

2.2.1 Sazonalidade do Estágio

O meu estágio, como já referido anteriormente, foi realizado de setembro a fevereiro, pertencendo este período maioritariamente aos meses do outono e inverno. Esta sazonalidade, faz com que as necessidades mais expressivas no atendimento sejam muito semelhantes.

As condições secas e frias associadas a estas estações, são as principais causas do aumento das infeções do trato respiratório, dado que para além de enfraquecerem o sistema imunitário da população, o frio é um facilitador visto que aumenta a sobrevivência dos vírus respiratórios.[10]

Com isto, uma grande parte dos atendimentos nesta época são muito semelhantes, baseando-se na procura assídua de antigripais, descongestionantes, multivitamínicos, pastilhas para a garganta, xaropes para a tosse, cremes e suplementos para o tratamento das frieiras, entre outros. Adicionalmente, a pandemia que vivemos, veio exacerbar esta procura,

principalmente numa abordagem preventiva, dos produtos indicados como referência, no tratamento da sintomatologia associada ao Covid-19.

2.2.2 Dificuldade na associação nome comercial – Denominação Comum Internacional (DCI)

Enquanto estagiária, a associação do nome comercial à denominação comum internacional (DCI) foi a minha maior dificuldade durante as primeiras semanas em que estive nos atendimentos. Apesar do primeiro mês de estágio acabar por ser uma familiarização dos nomes comerciais, da cor das caixas e respetiva associação com a denominação comum internacional (DCI), a realidade é que o elevadíssimo número de medicamentos que nos passam pelas mãos, torna impossível memorizar na totalidade os mesmos.

Contudo, com o passar do tempo, o inerente contacto constante com essas moléculas tornou todo o processo muito mais natural, e consequentemente mais rápido.

2.3 Oportunidades (*Opportunities*)

2.3.1 Participação em formações internas

O papel do farmacêutico comunitário é, como já referido, essencial para a passagem de informação atualizada e com qualidade aos utentes. Desta forma é necessário que os mesmos tenham à sua disposição diversas formações, de diversas marcas, de modo a manterem os seus conhecimentos atualizados, corretos e inócuos.

Das inúmeras oportunidades que este estágio me ofereceu, no meio da farmácia comunitária, esta foi uma das que eu mais valorizei. Senti que o meu crescimento foi exponencial e conciso no que toca a atualização científica e técnica. Tive oportunidade de assistir a dezenas de formações, como por exemplo, em marcas de dermocosmética, entre as quais: Esthederm®, SVR®, Caudalie®, Uriage®, La Roche Posay®, Vichy®, Lierac®, Apivita®, Avène® etc. Apesar de a grande fatia pertencer a formações na área da dermocosmética, também tive a oportunidade de presenciar formações noutras áreas, como por exemplo, a suplementação alimentar.

Muitas destas formações eram on-line e podiam ir de meia hora a uma hora e meia, onde eram apresentadas várias dicas essenciais na indicação farmacêutica, vantagens sob outros produtos equiparáveis ou simplesmente a promoção de um novo produto prestes a ser lançado no mercado.

Neste contexto, estas formações foram um auxílio de notória importância no meu crescimento enquanto futura profissional, permitindo-me ter uma abordagem com o cliente muito mais segura e cientificamente preenchida.

2.3.2 Participação em campanhas de *marketing*

O objetivo do *marketing* é promover produtos de forma a gerar receita para a empresa em questão. Existem diferentes maneiras de fazer *marketing*, um deles, que é sem dúvida onde recai a maior percentagem hoje em dia, é a criação de conteúdos digitais, mais concretamente, o *marketing* digital.

A FF promove muitos produtos e serviços através das diferentes plataformas digitais que possui.[11,12] Uma das plataformas que se encontra em constante movimento é o *Instagram*, onde semanalmente são feitas publicações com o objetivo de promover algum produto novo no mercado, divulgar alguma promoção que esteja a decorrer, uma presença de uma conselheira de uma marca na farmácia, etc. Com isto, tive a oportunidade de criar alguns conteúdos com esse mesmo efeito (Anexo 3 e 4), onde me foi concedida total liberdade para explorar a melhor maneira de realizar esta tarefa.

Dentro do *marketing*, destaca-se uma ferramenta essencial, desde que entramos na farmácia até que saímos, que consiste no *Merchandising*. O *Merchandising*, no contexto de indústria farmacêutica, consiste num conjunto de técnicas, colocadas em prática no ponto de venda, com o objetivo de aumentar a rentabilidade e a rotação de produtos acordados entre o distribuidor e o vendedor, que neste caso é a farmácia.[13] Neste contexto, foi me pedido que criasse um conteúdo para colocar junto do produto no linear, cujas informações a colocar, estavam previamente acordadas com a respetiva indústria (Anexo 5).

Descobri com esta experiência, mais uma função do farmacêutico comunitário que desconhecia dentro da sua prática, e do impacto da mesma na farmácia enquanto empresa.

2.4 Ameaças (*Threats*)

2.4.1 Medicamentos Esgotados

Apesar da FF ser conhecida por deter um largo *stock* de medicamentos de vários laboratórios, inclusive os medicamentos mais raros e dispendiosos, existiram situações de descontentamento por parte dos utentes devido ao facto de não conseguirem junto da farmácia, adquirir o que procuravam e precisavam, onde nem data de previsão conseguíamos

conceder. Recordo o caso do Victan® 2mg, substância ativa loflazepato de etilo, classificado como uma benzodiazepina, encontrando-se indicado para crises de ansiedade.[14]

A indisponibilidade prolongada deste medicamento a nível nacional originou uma grande preocupação e ansiedade por parte dos utentes, o que também trouxe desconforto e preocupação para a farmácia e respetiva equipa técnica.

2.4.2 Espaços de venda de MNSRM

Os espaços de venda de medicamentos não sujeitos a receita médica (MNSRM) são locais de venda previstos conforme o Decreto-Lei n.º 134/2005, de 16 de agosto.[15] Esta lei veio permitir que esta classe de medicamentos pudessem ser adquiridos fora da farmácia, deixando de ser este, um local exclusivo aquando da procura dos mesmos.

Esta lei provocou uma enorme convulsão no sector farmacêutico, principalmente a nível económico. Em grandes superfícies, como é o caso do centro comercial onde está inserida esta farmácia, é onde se acentua mais este problema, que gera uma competição pelo cliente, que prefere sempre o serviço com o preço de venda ao público (PVP) mais em conta. E enquanto a diferença de PVP entre farmácia e parafarmácias não revela grande disparidade, o mesmo não acontece com os supermercados, onde os preços praticados sofrem uma diminuição de 20%.[16]

Tive oportunidade de verificar esta situação quando em conversa com alguns utentes, verifiquei que antes de efetuar a compra, optavam por aceder a outro estabelecimento de forma a verificar o preço praticado pelo mesmo e concretizar uma comparação direta dos mesmos. Verifiquei assim, variados casos onde os utentes não voltaram para concluir a compra devido à incomparável capacidade das grandes superfícies de exercer um PVP inferior.

2.4.3 COVID-19

A pandemia da Covid-19 criou um constrangimento na grande parte dos setores, o da saúde não foi exceção. Nos meses em que o meu estágio se inseriu houve diversas fases, estipuladas pelo governo, onde muitas eram regidas por horários reduzidos do setor comercial.[17,18] Deste modo, estando a FF inserida num centro comercial, houve uma diminuição acentuada no número de atendimentos, e consequentemente no número de vendas neste estabelecimento.

Para além do impacto económico, a pandemia veio acentuar o papel da farmácia enquanto primeiro e, muitas vezes único contacto dos cidadãos com o sistema de saúde. Durante os

diversos atendimentos que fui fazendo, verifiquei em alguns casos de utentes com quadros de sintomatologia da Covid-19, a vir ao auxílio da farmácia. Este comportamento reflete uma atitude negligente e totalmente desinformada no que concerne às normas estabelecidas pelo governo a fim de conter a pandemia atualmente vivida, ameaçando paralelamente a minha segurança, dado esta procura poder resultar num contágio direto para mim enquanto profissional.

Com isto, a pandemia em que vivemos presentemente e onde o meu estágio esteve enquadrado, afetou de diversos modos o meu estágio, havendo inclusivamente a possibilidade de uma interrupção do mesmo por tempo indefinido

2.4.4 Tentativa de compra de MSRM sem receita médica

Ao longo deste estágio, a carência pelo conhecimento básico das leis estabelecidas relativamente à dispensa de medicamentos foi ficando cada vez mais exposta para mim. Onde esta desinformação é mais marcada, no espaço de farmácia comunitária, é relativamente à dispensa de medicamentos sujeitos a receita médica (MSRM), que carecem de uma maior preocupação e de uma legislação mais apertada. Entre as razões para esta preocupação na dispensa destes medicamentos, estão as de segurança para o utilizador, dado tratar-se de medicamentos que podem constituir direta ou indiretamente um risco, caso sejam utilizados sem vigilância médica.[19]

Diariamente, era abordada por vários utentes, cuja sua intenção primária era adquirir um MSRM sem a respetiva receita. Uma parte deste grupo de utentes, afirmavam desconhecer tal estatuto do medicamento em causa e após breve esclarecimento, compreendiam a impossibilidade de aceder ao seu pedido. Com isto, havia clientes que optavam por, ou entrar em contacto com o seu médico, ou pedir um aconselhamento nos casos onde era possível, de forma a adquirir uma alternativa junto dos MNSRM.

Todavia, existiram variados casos de utentes que entraram em conflito verbal, usando diversos argumentos nomeadamente como, "na outra farmácia sempre me venderam esse medicamento sem receita" ou como "não tenho receita, mas já tomei isso em tempos".

Na minha opinião a população em geral sofre de um elevado grau de desinformação em relação à legislação, tornando-se esta falta de conhecimento numa ameaça para o trabalho do farmacêutico comunitário.

3. Casos Práticos

3.1 Caso Prático 1

A utente A, do sexo feminino e com cerca de 35 anos, dirigiu-se à farmácia para tentar resolver um problema relacionado com a sua pele. Queixa-se do aparecimento de acne, e explica que a está a deixar transtornada, pois achava que era algo característico da adolescência e não na idade adulta. Antes de aconselhar a utente expliquei que, infelizmente, o acne adulto existe e não é tão incomum como a senhora achava.

Inicialmente, inquiri em relação aos cuidados diários que tinha com a sua pele e se usava produtos cosméticos, se sim quais e de que marca. A utente disse que usava pontualmente um creme hidratante básico que costuma obter no supermercado e que nunca se tinha preocupado muito com o cuidado da sua pele.

Após breve análise da descrição feita pela utente, entendi que seria necessário exercer uma breve explicação dos cuidados básicos que todas as peles devem ter. Todos os dias de manhã e à noite, a pele deve ser limpa antes de qualquer tipo de cuidado e regra geral, uma pele oleosa com tendência acneica, tem preferência por uma galénica fresca e não muito pesada como um gel de lavagem ou uma água micelar. De seguida, conforme as necessidades e o que a pessoa procura corrigir na sua pele, deve ser aplicado por ordem decrescente de fluidez, todos os restantes cuidados, como creme de olhos, sérum, creme e protetor solar.

Posteriormente, dirigi-me ao linear pertencente à marca SVR® e iniciei o meu aconselhamento, que acredito ter sido o mais indicado para esta situação. Indiquei como cuidado de limpeza a água desmaquilhante da gama "Sebiaclear",[20] visto que a senhora utiliza maquilhagem frequentemente. Deste modo, é possível obter um efeito duplo e sinérgico onde a remoção da maquilhagem trata simultaneamente da limpeza e purificação da pele. Esta água é composta essencialmente por gluconolactona, responsável pela purifcação e desobstrução dos poros, e por micelas que limpam e removem a maquilhagem. Após a limpeza, aconselhei a utilização como cuidado diário, de manhã e à noite, do sérum "Sebiaclear".[21] Este sérum foi especialmente desenhado para o tratamento do acne adulto, uma vez que possui um ativo completo antienvelhecimento, constituído por ácido hialurónico e retinoid-like que ajudam no combate aos sinais de envelhecimento, suavizando e preenchendo as rugas, e também um poderoso duo de anti-imperfeições formado por gluconolactona e niacinamida, permitindo resolver o acne adulto ao mesmo tempo que corrige os sinais de envelhecimento.

3.2 Caso Prático 2

O utente B, do sexo masculino e com cerca de 40 anos, refere que vai fazer uma viagem longa de trabalho de autocarro, e como costuma enjoar, precisa de algum medicamento de forma a evitar o enjoo.

Pergunto-lhe se toma alguma medicação, ao que o utente responde que não. Faço uma breve avaliação da situação, e defino-o como um enjoo associado ao movimento. Falo ao utente de todas as medidas não farmacológicas a tomar, que consistem em evitar alimentos ricos em gordura e líquidos em excesso antes da viagem. Em termos de medidas farmacológicas, aconselho Vomidrine®, um antagonista dos recetores H1, indicado para os vómitos associados ao movimento.[22] Refiro igualmente que a sonolência, as tonturas e zumbidos são os efeitos secundários mais associados a este medicamento, e que por essa razão, podem se manifestar após a toma. Termino o atendimento indicando a posologia, referindo que deve tomar um comprimido meia hora antes de proceder à viagem.

3.3 Caso Prático 3

A utente C, do sexo feminino e com aproximadamente 30 anos, dirigiu-se à farmácia à procura de um medicamento para a dor de cabeça. Afirma sentir um peso nos olhos e associado a isso refere que está congestionada. Como é típico da altura do ano, associei rapidamente a um quadro típico de sinusite.

A utente referiu que não queria nada muito forte e o "mais natural possível". Perante este pedido, lembrei-me de apresentar como solução uma medida não farmacológica, a lavagem nasal, que mostra ser bastante eficaz quando bem aplicada.

Trouxe ao balcão o sistema de irrigação da Nasopure®, que ajuda na prevenção e alívio dos sintomas associados à sinusite. A utente referiu que nunca tinha usado, mas que estava disposta a experimentar. Procedi a uma breve explicação de como o sistema funciona, onde elucidei como fazer o preparado, e das instruções que se seguem em relação ao procedimento da lavagem em si.

4. Conclusão

Do ponto de vista da saúde pública, as farmácias são locais de extrema importância, onde em grande parte dos casos é feita a primeira procura de ajuda, e onde muitas vezes se propicia a entrada de utentes no sistema de saúde. Em regra, os farmacêuticos comunitários são os agentes de saúde mais disponíveis para a população geral.

Este tipo de perspetiva foi-me clarificado, aquando da realização deste estágio, onde verifiquei a importância do papel de um farmacêutico comunitário. É uma profissão caracterizada pelas muitas exigências que acarreta, e também pelo vasto conhecimento necessário em diversas áreas do medicamento e não só.

A realização deste estágio transformou-se num ponto de viragem para mim, onde percebi que esta profissão é a ponte entre o mundo científico e a população. A existência desta ponte é de relevância extrema, pois ao contrário do que pensava previamente, a iliteracia na saúde ainda é notavelmente elevada.

A Farmácia do Forum prima pela equipa rigorosa de profissionais, cujo conhecimento científico me promoveu o constante interesse de querer saber mais e melhor. A bagagem que carrego agora, mais pesada após estes meses de estágio, deve-se à excelência desta equipa, que nunca esquecerei.

Termino esta etapa com a certeza, de que o meu percurso na Faculdade de Farmácia da Universidade de Coimbra, me deu as ferramentas necessárias, para me tornar numa farmacêutica onde o brio e o rigor na atividade que escolhi esteja espelhado.

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6. Anexos

Anexo I – Ficha de preparação de medicamentos manipulados – Suspensão oral de Enalapril 1mg/ 1mL

FARMÁCIA DO FORUM

Ficha de Preparação de Medicamentos Manipulados

Página 1 de 3

Medicamento: Suspensão oral de Enalapril 1mg/ml

Teor em substância(s) activa(s): 100 ml contém 100mg de maleato de enalapril

Forma farmacêutica: Suspensão oral

Data de preparação: 17/09/2020

Número do lote: 88/2020

Quantidade a preparar: 100ml

Matérias-primas	Lote nº	Origem	Farmacopeia	Quantidade para 100 g (ou ml, ou unidades)	Quantidade calculada	Quantidade pesada	Rubrica do Operador e data	Rubrica do Supervisor e data
Renitec® 20mg (maleato enalapril)	T000622	MSD	PT	100mg	100mg	100mg (5 comp.)		17/09/20
SyrSpend® ph4 cereja	200002221	Fagron	PT	qb 100ml	qb 100ml	qb 100ml		

Preparação

	Rubrica do Operador
1. Verificar o estado de limpeza do material.	
2. Pulverizar os 5 comprimidos de enalapril em almofariz de porcelana.	
3. Adicionar lentamente uma pequena porção de veículo (Syrspend®) até obtenção de um preparado homogéneo;	
4. Adicionar, em proporção geométrica o veículo (Syrspend®), agitando constantemente;	
5. Transferir para proveta, agitando constantemente;	
6. Lavar o almofariz com o veículo e juntar à proveta;	
7. Completar o volume;	
8. Agitar;	
9. Rotular.	

Embalagem

Tipo de embalagem: Frasco de vidro âmbar tipoIII

Capacidade do recipiente:

Material de embalagem	Nº do lote	Origem
Frasco de vidro âmbar tipo III 100ml		

Operador:

IMP.10.2

Prazo de utilização e Condições de conservação

Condições de conservação: Em recipiente bem fechado, à temperatura ambiente. Operador: [redacted]
Prazo de utilização: 90 dias Operador: [redacted]

Verificação

ENSAIO	ESPECIFICAÇÃO	RESULTADO	Rubrica do Operador
Odor	A cereja	Conforme	[redacted]
Cor	Alaranjado	Conforme	[redacted]
Aspecto	Homogéneo	Conforme	[redacted]
pH	4	Conforme	[redacted]

Aprovado ☑ Rejeitado ☐

Supervisor: [redacted] 17/09/20

Nome, morada e telefone do doente

[redacted]

Nome do prescritor

[redacted]

Anotações

FARMÁCIA DO FORUM

Ficha de Preparação de Medicamentos Manipulados

Cálculo do preço de venda

MATÉRIAS-PRIMAS:

matérias-primas	embalagem existente em armazém		preço de aquisição de uma dada quantidade unitária (s/IVA)		quantidade a usar	factor multipli-cativo	valor da matéria-prima utilizada na preparação
	quantidade adquirida	preço de aquisição (s/IVA)	quantidade unitária	preço			
Renitec® 20mg	56comp.	5.14€	1comp.	0.0918€	5		0.4589
Syrspend® ph4 cereja	473ml	30.42€	1ml	0.0643€	100ml	1.6	10.288
						subtotal A	**10.7469**

HONORÁRIOS DE MANIPULAÇÃO:

	forma farmacêutica	quantidade	F (€)	factormultiplicativo	valor
valor referente à quantidade base	**Suspensão**	100ml	3	5.05	15.15
Valor adicional					
				subtotal B	**15.15**

MATERIAL DE EMBALAGEM:

materiais de embalagem	preço de aquisição (s/IVA)	quantidade	factor multiplicativo	valor
Frasco de vidro ambar 100ml	0.49	1	1,2	0.588
			subtotal C	**0.588**

PREÇO DE VENDA AO PÚBLICO DO MEDICAMENTO MANIPULADO:	**(A + B + C) x 1,3**	34.43€
	+ IVA	2.07€
	D	36.50€

DISPOSITIVOS AUXILIARES DE ADMINISTRAÇÃO:

dispositivo	preço unitário	quantidade	valor
		E	
		PREÇO FINAL: D+E	**36.50€**

Operador: _____ Supervisor: _____

Rubrica do Director Técnico	Data
Laura Pa	17/09/20

IMP.10.2

Anexo 2 – Rótulo do manipulado – Suspensão oral de Enalapril 1mg/ 1mL

FARMÁCIA DO FORUM

MANIPULADO: Suspensão Oral de Enalapril 1mg/ml; 100ml

DATA: 17/09/2020 **PRAZO DE UTILIZAÇÃO:** 17/12/2020

LOTE: 88/2020 **PREÇO:** 36.50€

UTENTE: [redacted]

POSOLOGIA: 1 ML À NOITE

CONSERVAÇÃO: À temperatura ambiente, em recipiente bem fechado. Agitar muito bem antes de administrar.

DIRECÇÃO TÉCNICA DRA. LAURA MARIA DOS SANTOS COELHO

C.C.FORUM COIMBRA, LJ 043 – 3040-389 COIMBRA – T 239800610

Anexo 3 – Campanha de *Marketing* – promoção Aveeno® e Neutrogena®

Anexo 4 – Campanha de *Marketing* – novidades Uriage e Apivita

Anexo 5 – *Merchandising* – Gurosan®

MONOGRAFIA

"ENDOCRINE DISRUPTORS PRESENT IN FOOD AND THEIR ROLE IN FEMALE INFERTILITY"

-

Orientado pela Professora Doutora Ana Teresa Sanches Silva

Abstract

According to the World Health Organization (WHO), infertility is a public health problem that affects around 48 million couples and 186 million individuals worldwide. Many reasons with different natures are behind this, endocrine disruptors (EDs) are one of the reasons that raise more concern, given that it is a problem that has evolved with the progress of society. Many types of chemicals are used in the food industry, which can easily enter the food chain, directly affecting human health, and remain ubiquitous in the population. Endocrine disruptors have the capacity of interfering with the normal hormonal action, metabolism, and biosynthesis, which can lead to a variation of the normal hormonal homeostasis. Bisphenol A (BPA) and its metabolites, phthalates, dioxins, organochlorine, and organophosphate compounds are groups of chemicals considered to have the capacity to disrupt endocrine activity. Some of these effects have already been characterized in experimental studies with animals and humans, and in clinical trials. Even though is not considered to be consistent alongside the scientific society, some of these endocrine disruptors are highly associated with diseases that are positively correlated with both male and female infertility. In this review, special focus will be given to female infertility, where diseases such as polycystic ovary syndrome, endometriosis, and also disturbances on processes as steroidogenesis and development of the ovarian follicles are highly associated with endocrine disruptors.

Keywords: Endocrine disruptor, Female infertility, Food exposure, Bisphenol A, Phthalates, Dioxins, Organochlorine and Organophosphate compounds.

Resumo

Segundo a Organização Mundial da Saúde, a infertilidade é um problema de Saúde Pública que afeta cerca de 48 milhões de casais e 186 indivíduos em todo o mundo. Muitos motivos de diferentes naturezas estão por trás deste problema, sendo os desreguladores endócrinos um dos que levanta mais preocupações, dado que se trata de uma problemática que tende e evoluir com a evolução da própria sociedade. Muitos tipos de químicos são utilizados na indústria alimentar, podendo facilmente entrar na cadeia alimentar, afetando diretamente a saúde humana, e permanecendo omnipresentes na população. Os desregulados endócrinos têm a capacidade de interferir na ação hormonal normal, no metabolismo e na biossíntese, o que pode levar a uma alteração da homeostase hormonal normal. O bisfenol A e os seus metabolitos, os ftalatos, as dioxinas, e os compostos organoclorados e organofosforados são grupos de compostos considerados por ter a capacidade de perturbar a atividade endócrina. Alguns desses efeitos já foram caracterizados em estudos experimentais em animais e humanos, e em ensaios clínicos. Embora não haja consistência dentro da sociedade científica, alguns destes desreguladores endócrinos estão intimamente associados a doenças positivamente correlacionadas tanto como a infertilidade masculina como a feminina. Nesta revisão, especial foco vai ser dado à infertilidade feminina, onde doenças como a síndrome dos ovários policísticos, a endometriose e também com alguns distúrbios em processos como a esteroidogénese e o desenvolvimento de folículos ovários estão altamente associadas a desreguladores endócrinos

Palavras-chave: Desreguladores Endócrinos, Infertilidade feminina, Exposição alimentar, Bisfenol A, Ftalatos, Dioxinas, Compostos organoclorados e organofosforados.

List of Abbreviations

AhR - Aryl-hydrocarbon receptor

AR - Androgen receptor

BPA - Bisphenol A

BPE - Bisphenol E

BPF - Bisphenol F

BPS - Bisphenol S

DBP - Di-n-butyl phthalate

DDT - Dichlorodiphenyltrichloroethane

DEHP - Di(2-ethylhexyl) phthalate

DHA - Docosahexaenoic acid

DiBP- Di-iso-butyl phthalate

DZN- Diazinon

EDs - Endocrine disruptors

EFSA - European Food Safety Authority

EPA - Eicosapentaenoic acid

ER - Estrogen receptor

FGSCs - Female germline stem cells

FSH - Follicle-stimulating hormone

GnRH - Gonadotropin-releasing hormone

HPG - Hypothalamic–pituitary–gonadal

HPO - Hypothalamic-pituitary-ovarian

IARC - International Agency for Research on Cancer

LH - Luteinizing hormone

MBP - Mono-n-butyl phthalate

MBzP - Monobenzyl phthalate

MCNP - Monocarboxyisononyl phthalate

MCOP - Monocarboxyisooctyl phthalate

MCPP - Mono(3-carboxypropyl) phthalate

MECPP - Mono(2-ethyl-5-carboxypentyl) phthalate

MEHP - Mono-2-ethylhexyl phthalate

MEOHP - Mono(2- ethyl-5-oxohexyl) phthalate

MEP - Monoethyl phthalate

MiBP - Mono-isobutyl phthalate

MiBP - Mono-iso-butyl phthalate

OCPs - Organochlorine pesticides

OPs - Organophosphate pesticides

PCBs - Polychlorinated biphenyls

PCDDs - Polychlorinated dibenzo-p-dioxins

PCDFs - Polychlorinated dibenzofurans

PCOs - Polycystic ovary syndrome

POPs - Persistent organic pollutants

PR - Progesterone receptor

PVC - Polyvinyl chloride

SML - Specific Migration Limit

SWHS - Seveso Women's Health Study

TCDD - 2,3,7,8-tetrachlorodibenzo-p-dioxin

TTP - Time to pregnancy

WHO - World Health Organization

1. Introduction

Infertility is a global public health problem that affects around 8 to 12% of couples in reproductive age worldwide. According to the WHO, infertility is defined as "*a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse*".[1] It has a huge impact on the population in cause since the couples can experience depression, anxiety, distress, reduced self-esteem, and a feeling of guilt and blame during the process.

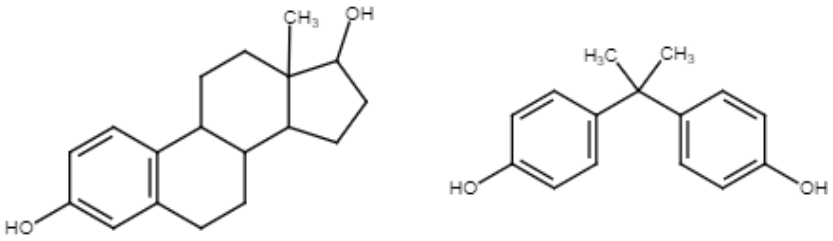
There is a growing interest in the role that EDs can play in Public Health, namely in reproductive female health. The recent changes in the lifestyle of individuals and societies are the major factor that contributes to the higher exposure to these harmful chemicals. These substances are increasingly present in our environment, in our food and food packages and, in consumer products (cosmetic, daily use, etc.).

The scientific community is quite unanimous regarding the definition of endocrine disruptors, "*an endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*".[2] The European Chemical Agency alongside with European Food Safety Authority (EFSA) has published in 2018 a guidance document for the identification of endocrine disruptors.[3]

The present literature review covers various aspects of the possible relationship between endocrine disruptors and female infertility. The main groups of endocrine disruptors associated with female infertility are herein addressed, including BPA, phthalates, dioxins and dioxin-like compounds and organochlorine and organophosphate pesticides. Moreover, the most common analytical techniques used for their determination were discussed. Finally, the results reported in *in vivo* studies and in clinical trials addressing endocrine disruptors and female infertility were covered as well as their possible mechanism of action.

2. Endocrine disruptors

Endocrine disruptors, also called endocrine active substances, endocrine disrupting chemicals or endocrine disrupting compounds are chemicals with the ability to interfere with normal hormonal action leading to adverse health effects. These abnormal activities can result in many adverse health effects since they interfere with natural hormone systems and its respective maintenance of the normal pathway of body hormones.

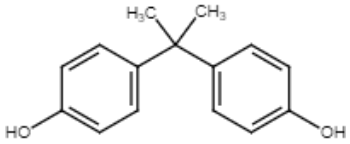
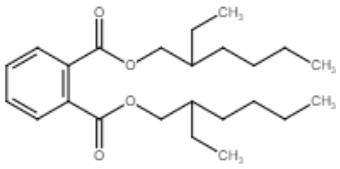
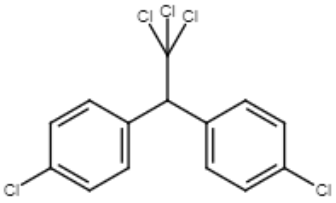
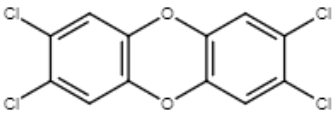


Estradiol Bisphenol A

Figure 1: Example of an analogy of the chemical structures of the natural estrogen hormone estradiol and bisphenol A, a xenoestrogen endocrine disruptor.

There are many different sources of the different chemicals with endocrine disruptive activity. In this work, three major groups of endocrine active substances that have a more distinguished role on female health will be explored, since they are often referred as food contaminants. Plasticizers, like bisphenol A (BPA) and phthalates, are one of the major families of chemicals that can be found frequently in food packaging industries and can be easily identified in contamination processes. Another vast group is pesticides, more specifically organophosphate and organochloride compounds that are also very linked to adverse reproductive effects. Finally, we have dioxin and dioxin-like compounds that emerge very frequently from uncontrolled incinerations, accidental fires, and waste burning, where the principal source of human contamination is through food and through environment.

Table 1: Classifications, chemical properties, and sources of the most common EDs.

EDC	General Chemical Structure	Group	Route of exposure	Sources	Half-life
BPA		Bisphenols/ Plasticizers	Ingestion, inhalation, dermal absorption	Polycarbonate plastics, thermal paper, epoxy resins, plastic toys, and bottles, lining of food cans.	4-5 hours
DEHP		Phthalates/ Plasticizers	Ingestion, inhalation, dermal absorption	Medical devices, artciles made of PVC.	4-8 hours
DDT		Organochloride/ Pesticides	Ingestion, inhalation, dermal absorption	Contaminated water, soil, fish.	6-10 years
TCDD		Dioxin	Ingestion, inhalation	Combustion of fossil fuels, incineration processes.	1.6-3.2 years

Note: BPA: Bisphenol A; DEHP: Di(2-ethylhexyl) phthalate; DDT: Dichlorodiphenyltrichloroethane; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; PVC: Polyvinyl chloride.

2.1 Endocrine disruptors associated with female infertility

EDs appear to have a role that negatively affects female infertility, examples of well-known EDs for this negative effect are present in Table 1. An increasing number of papers aim to explain and explore the aspects involving this activity and its role on reproductive health. Since the chemical structure of most EDs mimics sex gonadal hormones (e.g. Figure 1), the reproductive system is the most vulnerable system to EDs actions. They have the ability to bind to endocrine receptors and interfere with hormonal signals, representing a threat to the normal function of the endocrine system.

The mechanisms by which these compounds act, are still one of the major concerns to be solved. Most EDs have synergistic or antagonistic outcomes, and many can interfere with estrogen receptors (ER) or androgen receptors (AR), aryl hydrocarbon receptor (AhR) is the most studied protein concerning its activity with EDs.[4]

2.1.1 Bisphenol A

BPA is an industrial substance widely present in daily life, mainly in plastic materials. Among the numerous exposures possible from this compound, food exposure is the one that brings more concern, being the one that reaches the greatest number of people which can occur for a long time without being detected. It is used to produce synthetic polymers, including epoxy resins and polycarbonate, which are used in reusable bottles, kitchen utensils, varnishes and protective coatings for canned food and beverages.[5]

The specific migration limit (SML) of BPA has decreased from 0.6 mg/kg food to 0.05 mg/kg food. This alteration was established on the regulation 2018/213, modifying the previous SML foreseen on the regulation (EU) N° 10/2011.[6] The main dietary source of exposure to BPA are canned food, meat products, and fish can also show high levels of BPA.[7]

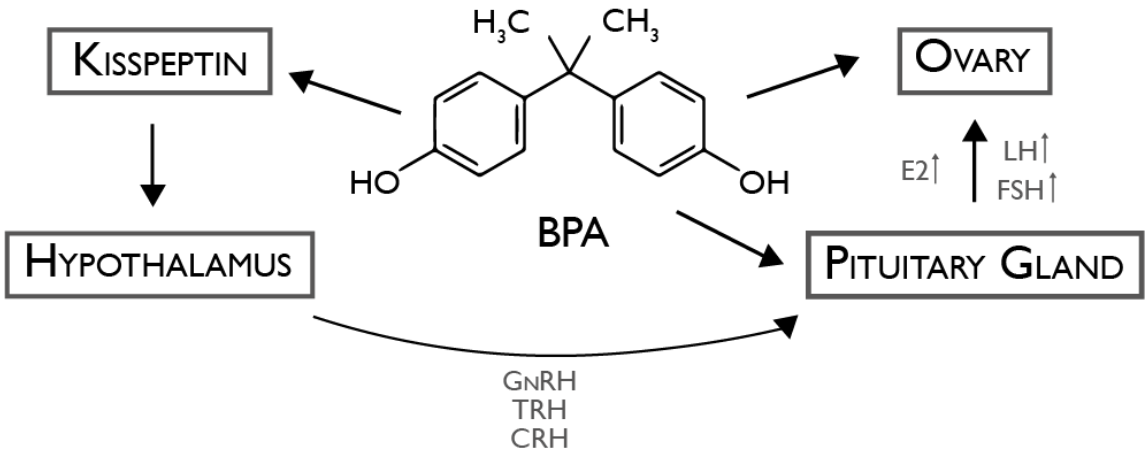


Figure 2: Disruptive mechanism induced by BPA on HPG axis. BPA regulating kisspeptin expression leads to alterations in GnRH levels, affecting the release of FSH, LH, and sex hormone, resulting in adverse effects on the reproductive system. (Adapted from Ma *et al.*[8])

BPA can disrupt at many levels, the feedback control system including hypothalamic–pituitary–gonadal (HPG) axis is one of them (Figure 2), being the reason why this ED is closely connected to reproductive health. On the HPG axis there is evidence that this chemical can alter the levels of Gonadotropin-releasing hormone (GnRH), regulating kisspeptin expression. This alteration traduces in the release of Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), and sex hormone, which results in adverse effects on the reproduction system via irreversible impairment of the HPG axis.[8]

The International Agency for Research on Cancer (IARC) has designed a system to categorize different agents and their carcinogenicity to humans. Based on this classification BPA is inserted in group 2A- "Probably carcinogenic to humans".[9] This designation is attributed when a component lacks evidence of carcinogenicity in humans but, in animals experiments, there is strong and sufficient evidence of the carcinogenicity, and that the mechanistic in cause also runs in human organism.[10]

2.1.2 Phthalates

Another group of substances used in the plastic industry is phthalates. It is estimated that 4,9 billion kilograms are the global production of this plasticizer per year.[11]

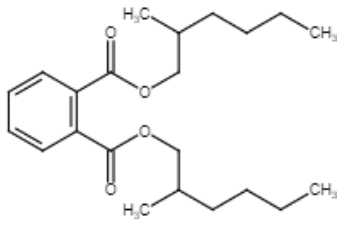
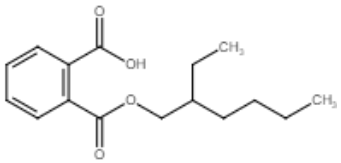
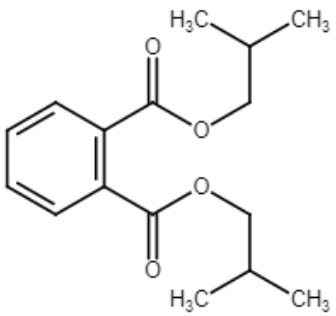
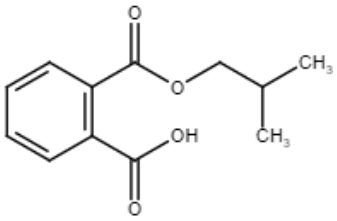
Phthalates are used to make the plastic more malleable, more transparent, and with larger durability. They are considered endocrine disruptors since they have the capacity to interfere with biosynthesis, metabolism, and hormonal activity, changing the natural way of our hormonal system.[12]

There is a growing concern about the role that phthalates play in fertility. Some of them had already been characterized as toxic substances for reproduction and because of that, some restrictions have been made on the industry.[13]

It is unquestionable that the production of polyvinyl chloride (PVC) is the most common use of phthalates. PVC is an extensively used plastic around the world, and it is present in numerous products present in our daily life. Examples of that are food packaging and packaging in general, manufacture of toys, certain pharmaceutical formulations and thousands of consumer goods.[13]

A very extensive and robust study was carried out in order to analyze the presence of phthalates in food and beverages, such as those included in Table 2, and also highlights the many different toxic effects that these chemicals may perform on human health, namely the adverse effects on reproductive health. What arises from all the different analyses on the different groups of food and beverages, was that there are a lot of factors that contribute to the migration of these chemicals from packaging into food. Another conclusion was that alongside the evolution of the food chain is the increase of the phthalates concentration.[14]

Table 2: Principal phthalates that had been demonstrated to interact with estrogen receptor and progesterone receptor (PR) in humans.[14]

Parent Phthalates (Phthalate-diester)	**Primary Metabolites (Phthalate-monoester)**
DEHP 	MEHP 
DiBP 	MiBP 

Note: DEHP: Di(2-ethylhexyl) phthalate; MEHP: Mono-2-ethylhexyl phthalate; DiBP: Di-iso-butyl phthalate; MiBP: Mono-iso-butyl phthalate.

Di(2-ethylhexyl) phthalate (DEHP) is one example of a high-molecular-weight phthalate and one of the most studied phthalates. It is mostly used as a plasticizer in the production of PVC. This phthalate formerly had been classified as possibly carcinogenic, however, according to the most recent IARC evaluation DEHP "is not classifiable as to its carcinogenicity to humans (Group 3) because peroxisome proliferation has not been documented in human hepatocyte cultures exposed to DEHP nor in the liver of exposed non-human primates. Therefore, the mechanism by which DEHP increases the incidence of hepatocellular tumors in rats and mice is not relevant to humans".[15]

For the past years, the effects of phthalates in the male reproductive system were much more documented and explained than the effects on the female reproductive system. Nowadays is clear that phthalates play a severe role in both genders.[16] The disruptive mechanism behind this class of EDs is not fully understood, nevertheless, disorders on the HPG axis have been associated with some phthalates, which is crucial to develop a correct reproductive development.[17] The mechanism involved is still uncertain, nevertheless, studies have revealed the structure dictates the response that will be triggered, that is, it can have an inhibitory or stimulating response on the AR and ER activity. For example, it was shown that DEHP, and its respective metabolites, do not bind to AR.[18]

2.1.3 Dioxins and dioxin-like compounds

The term dioxin is applied for a group of 210 chlorinated compounds which divides into two subgroups, the polychlorinated dibenzofurans (PCDFs) and the polychlorinated dibenzo-p-dioxins (PCDDs). Within these 210 compounds, the 17 congeners with chlorine atoms at the 2,3,7 and 8 positions are found to be of major importance once this characteristic gives them a more resistant metabolic degradation, which results in body accumulation.[19]

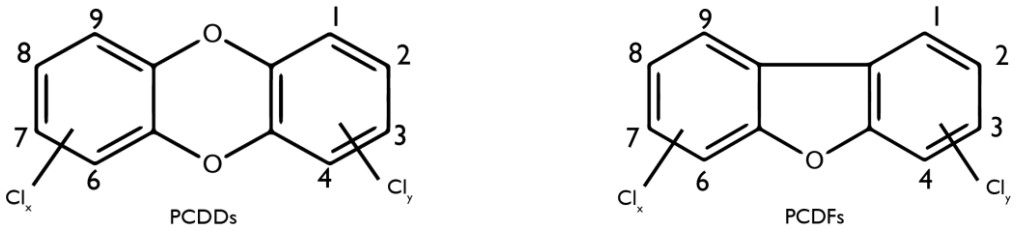


Figure 3: Structure of dioxins (PCDDs and PCDFs). Relevant PCDD/Fs are substituted with additional chlorines at positions 2,3,7 and 8.

Dioxins are dangerous environmental pollutants that belong to a group called Persistent Organic Pollutants (POPs). The interest in this group, to the scientific community, has been growing due to their toxic effects on animals, the environment, and human health.[20]

The main source of dioxins is anthropogenic especially due to combustion processes but can also emerge due to natural processes. The formation occurs at high temperatures between organic compounds and chlorine. Another huge source of dioxins is uncontrolled waste incinerators.[21] Although many of these releasing events of dioxins to nature are local, the spreading is global. According to the WHO "the highest levels of these compounds are found in some soils, sediments and food, especially dairy products, meat, fish and shellfish. Very low levels are found in plants, water and air."[20]

As mentioned, fatty food is an important source in terms of human exposure. A study conducted in Norway was performed in order to evaluate the risk-benefit of consumption of seafood, more specifically fish fillet, farmed salmon, wild mackerel, herring and spring spawning. Despite the important role as a huge supplier of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and vitamin D, it is also pointed out as a source of dioxins. It has been concluded that even with the high levels of EPA, DHA, and vitamin D, if the species were consumed according to the recommendations, the levels of dioxins consumed were exceeded.[22]

In the field of dioxin toxicology, even though the mechanism is not fully comprehended, is clear that these compounds induce various toxicities through their tight relation with the AhR. AhR is present in ovaries tissues and performs a starring role in the regulation of ovarian follicular growth and steroidogenesis.[23] This connection between AhR and dioxins triggers all the endocrine signaling routes that are mediated by the steroid hormones.[24]

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was classified in 1997 by the IARC as a group 1 carcinogen. This category "is used when there is sufficient evidence of carcinogenicity in humans".[25] A very high number of studies have proven that TCDD is a potent carcinogenic with vast mechanistic information indicating that this substance could disrupt multiple endocrine pathways through a mechanism involving AhR.[26]

2.1.4 Organochlorine and organophosphate pesticides

Pesticides are synthetic molecules that emerged with the aim of killing or repelling pests, fungi, insects, diseases from plants during their growth. Their use is growing stronger since the global market for these pesticides is steadily expanding.

Table 3: The most common organochlorine and organophosphate compounds, their chemical structure, use, and persistence. (Adapted from Jayaraj[34])

Chemical name	IARC group	Use	Persistence in environment	WHO classification based on rat oral LD50
DDT	Group 2A	Acaricide insecticide	High persistence Half-life: 2-15 years	Moderately hazardous
DDD	-	Insecticide	High persistence Half-life: 5-10 years	Acute hazard in unlikely
DDE	-	Insecticide	High persistence Half-life: 10 years	Slightly hazardous
Diazinon	Group 2A	Insecticide	Moderately persistence Half-life: 37-38 days	Moderately hazardous

Note: DDT: Dichlorodiphenyltrichloroethane; DDD: Dichlorodiphenyldichloroethane; DDE: Dichlorodiphenyldichloroethylene.

It has been studied that the long exposure to these compounds its dangerous even in very low doses, they have the power to affect the organism since that many of them play a role as endocrine disruptors.[27,28] Table 4 summarizes the four most commonly referred organochlorine and organophosphate compounds.

One specific group of pesticides, which is widely used, is organochlorine compounds (OCPs) that are environmental pollutants and known as carcinogenic chemicals. The organophosphate insecticides were created to replace the so relentless OCPs, since they were proven to have low persistence in the environment and a rapid breakdown.[29]

Dichlorodiphenyltrichloroethane (DDT) is one of the most studied substances since a huge number of hormone-related effects on wildlife have been attributed to it. It was created around 1940, initially used to combat insect-borne human diseases such as typhus and malaria. As one of the first synthetic insecticides was also effective for insect control and was extensively used during many years after that. Despite its abolishment around 1970, DDT remains relevant to living populations for many reasons, it is a persistent pollutant in the environment, so people worldwide continue to be exposed.[30]

Endocrine disruptors can alter the pathway of hormones, acting as agonist or antagonist. DDT (isomers and metabolites), as an organochlorine pesticide that has reported endocrine disruptive activity, has demonstrated its dangerous activity when binding with hormone receptors, such as AR, where displays an antagonistic role, and its capacity to increase the progesterone receptor in the ovary and uterus, also raises concerns.[31,32]

This insecticide was classified, by IARC evaluation, as a group 2A substance that is probably carcinogenic to humans. The mechanistic data provide strong support for the carcinogenicity findings of DDT.[33]

2.1.5 Parabens

Parabens are widely used, as efficient preservatives in the cosmetic industry, food, pharmaceutical products, and other products that care for their use as antimicrobial agents.

On a first approach, parabens were considered in this paper as a relevant endocrine disruptor to explore and study their possible role in female infertility. However, after a long search and study of diverse publications and studies, they were left out, because the most recent studies report that parabens are still considered safe to use since there is a lack of scientific evidence about their toxicity and endocrine disruption activity. Nevertheless, studying this class of substances is still necessary, to better address the scientific gaps and disagreements existing and to provide better and more exact answers.[35,36]

3. Infertility

Infertility is a worldwide problem that has a huge impact on families and communities. It is estimated that 48 million couples and 186 million individuals are affected by infertility globally. It is a disease that can affect both genders. Female infertility is a condition that happens due to disorders in the female reproductive system, such disorders can present as uterine, tubal, and ovaries disorders, and also can come from endocrine disorders that led to abnormalities of reproductive hormones.[1]

The first epidemiological study on infertility in Portugal concluded that 260 to 290 thousand couples are unable to have children. The prevalence of infertility throughout life, in Portugal, is about 9% (8.9%).[49]

When focusing on Europe in terms of fertility, Europeans have generally been having fewer children.

"The most widely used indicator of fertility is the total fertility rate: this is the mean number of children that would be born alive to a woman during her lifetime if she were to pass through her childbearing years conforming to the age-specific fertility rates of a given year". In 2018 the fertility rate in the Europe was calculated, 1.55 live births per woman were the result. The lowest fertility rate was 1.43 and it was registered in 2001 and while the highest rate was 1.57 in 2010.[50]

3.1 Main causes

There are many causes pointed as responsible for female infertility. For a normal function of the reproductive system, women need to have functioning ovaries, uterus, fallopian tubes, and a normal endocrine system. When something compromises one of these systems, fertility may be jeopardized.[51]

Hereupon infertility may be caused by tubal disorders, uterine disorders, among which endometrioses stand out, ovaries disorders, such as polycystic ovary syndrome (PCOS), and disorders that endanger the endocrine system and its normal function.[1,51]

Growing evidence proposes a possible connection between endometriosis and environmental pollutants, more specifically the ones with disruptive activity. Environmental pollutants, such as dioxins show strong evidence that this exposure can lead to diseases as endometriosis.[52]

Besides the conditions referred above, there are many risk factors that contribute in a very sharp way, such as smoking,[53] excessive alcohol drinking,[54] obesity,[55] and age[56]. Other curious studies reveal many other possible risks that can contribute to infertility itself, there are numerous publications about the role of vitamin D in female infertility, revealing that this vitamin is essential to the reproductive system, and without it, the fertility can be compromised.[57,58,59,60] Another interesting finding during this research was that, contrary to what most women think,[61] there is no evidence that the use of an intrauterine device can play a negative role in female fertility.[62,63]

4. Effects of endocrine disruptors on female fertility

Endocrine disruptors have gained a lot of attention from the scientific community in the past years. A lot of laboratory and human studies have been published regarding the numerous chemicals causing this dangerous endocrine activity. The health effects that these compounds cause, have been increasing alongside the publications, proving that can be responsible for multiple diseases.

The endocrine system has an essential role in many physiological systems since it is responsible for hormonal communication, which is based on the production and release of hormones from different glands in the bloodstream, which coordinates various functions in our body by carrying messages. Hormones are essential for many processes such as metabolism, development and growth, metabolism, and reproductive functions. When the hormonal imbalance is not accurate, health problems can arise due to these alterations in the number of hormones produced by the glands. Many things can affect this balance, and endocrine disruptors, as the name indicates, are one of the major responsible.

4.1 Plasticizers

Plasticizers are a class of dangerous chemicals that are very problematic since they are more and more present in many human contact sources. They are widely present in the food industry, and with the growth that it has been suffering from modernization, they are used in almost every process.

A wide range of plasticizers has been extensively studied because of their consistent presence in the daily life of consumers. BPA and phthalates are particularly emphasized within this class, due to their constant exposure through consumer products. Studies performed *in vivo,* and some clinical trials in different populations, have been crucial to the understanding of the different ways they can affect reproductive health.

The most common cause of infertility, as a result of anovulation, is PCOS and it is estimated to affect 6-9% depending on the used criteria.[77] Women that suffer from this condition, present a hormonal imbalance that interferes with reproductive processes.

Table 4: *In vivo* studies with plasticizers found in food.

Research design	Dosage regimen	Parameters monitored	Outcomes/Main conclusion of the study	References
Investigate ovarian folliculogenesis and steroidogenesis in adult female rat offspring born to mothers exposed to low doses of BPA	BPA50: 50mg/kg day; BPA0.5: 0.5mg/kg day	Estrous cycle; Average size of preantral and antral follicles	Folliculogenesis and steroidogenesis are targets of BPA within the ovary	SANTAMARÍA, Clarisa *et al.* (2015)[69]
Effect of a low dose of BPA on the reproductive axis of prepubertal female rats	0.1% ethanol or BPA in their drinking water	Hormone levels	LH and estradiol levels increased significantly meanwhile, FSH ones showed no significant changes. The number of primary, secondary, and atretic follicles increased and antral ones were decreased. Early exposure to a low dose of BPA disrupts the normal function of the reproductive axis in prepubertal female rats	GÁMEZ, J. M. *et al.* (2015)[70]
This study had the goal to study the BPA effects on the ovaries function and structure and also to access to the levels of expression of the genes related to follicle development	10 mg/kg, 40 mg/kg, and 160 mg/kg of BPA	Serum estradiol (E2) and progesterone (P4); Rat body weights and ovary coefficients; The number of follicles at different stages; Changes in the mRNA expression of FIGLA, H1FOO, and AMH genes; Changes in protein expression of FIGLA, H1FOO, and AMH genes	This study demonstrates the probable negative role that BPA plays in ovarian development, and how the genes related to follicle development can be part of these outcomes	LI, Yuchen *et al.* (2014)[71]
This study was performed to examine whether prenatal exposure to BPA analogs, BPE and BPS, negatively impacts female reproductive functions and follicular development using mice as a model	BPA, BPE or BPS (0.5, 20 or 50 μg/kg/day)	Serum levels of E2 (sensitivity 3 pg/ml) or testosterone (sensitivity 90 pg/ml)	Prenatal exposure to BPA analogs, BPE and BPS, have effects on fertility in later reproductive life probably due to the disruption of early folliculogenesis	SHI, Mingxin *et al.* (2019)[72]
Effects and potential mechanism of BPA on mouse ovarian follicular development and FGSCs	BPA (12.5, 25, and 50 mg/kg/day)	-	The effect of BPA on ovarian follicular development and FGSCs, especially the effect on FGSCs, suggests a novel mechanism of how BPA causes female infertility	ZHU, Xiaoqin *et al.* (2018)[73]
The aim of this work was to test the effect of chronically exposed female mice to a mixture of three phthalates and two alkylphenols from conception to adulthood at environmentally relevant doses	Two doses: 1 and 10 mg/kg body weight/d of the total mixture	Plasma hormonal levels; Reproductive endpoints; Histological evaluation of the number of preantral and antral follicles; RNA extraction and real-time polymerase chain reaction; Protein extraction and Western blotting	These results indicate that not only exposure but also its level is relevant to assess the effective contribution of EDs in the development of diseases	PATIÑO-GARĆIA, Daniel *et al.* (2021)[74]
To test whether DBP causes ovarian toxicity	DBP at 0.01, 0.1, and 1000 mg/kg/day	Estrous cyclicity; steroidogenesis; ovarian morphology; Apoptosis and steroidogenesis gene expression	A 10-day exposure to DBP disrupted reproductive processes in CD-1 mice; DBP exposure resulted in decreased circulating E2; Antral follicle numbers and apoptosis gene expression were altered at low doses; Estrous cyclicity and corpora lutea counts were altered at a high dose; DBP exposure resulted in altered steroidogenesis gene expression	SEN, Nivedita; LIU, Xiaosong; CRAIG, Zelieann R. (2015)[75]
Investigate the negative effects of DEHP exposure on oocyte development	DEHP (40 μg/kg body weight)	Cytoskeleton; apoptosis; ROS levels; epigenetic modifications; Protein Juno receptor	DEHP exposure reduced the maturation and fertilization capabilities of mouse oocytes by affecting cytoskeletal dynamics, oxidative stress, early apoptosis, meiotic spindle morphology, mitochondria, ATP content, Juno expression, DNA damage, and epigenetic modifications in mouse oocytes	LU, Zhenzhen *et al.* (2019)[76]

Note: BPA: Bisphenol A; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; E2: 17β-Estradiol; P4: Progesterone; BPE: Bisphenol E; BPS: Bisphenol S; FGSCs: female germline stem cells; EDs: Endrocine disruptors; DBP: Di-n-butyl phthalate; DEHP: Di(2-ethylhexyl) phthalate.

Some human studies (Table 4) demonstrate that elevated BPA concentrations are detected in adolescent girls, and women with PCOS, when compared to the control group, suggesting the potential role of this substance in this pathology.[78] Serum BPA level in market seller women with PCOS was evaluated, as well as metabolic and hormonal effects of this exposure, comparing to a control group, and a positive correlation has been demonstrated between the exposure and the PCOS physiopathology.[66] Another study was conducted on adolescents girls with PCOS, to observe the serum levels of BPA and its possible relationship with obesity. It was concluded that adolescents with PCOS had higher levels of BPA than the group control, independently of obesity, carrying again to the perspective that BPA can be part of the cause of PCOS.[64]

Table 5: Observational studies of plasticizers and fertility-related problems.

Participants/subjects and research design	Patients	Patient parameters	Outcomes/Main conclusion of the study	References
Investigate the role of BPA in the pathogenesis of PCOS and other metabolic parameters	112 girls with PCOS and 61 controls	Serum BPA and oral glucose tolerance test	Adolescents with PCOS presented higher BPA concentrations than controls and there was a significant relation with androgen levels	AKIN, Leyla *et al.* (2014)[64]
To investigate possible associations between reproductive hormone levels among woman exposed to BPA	106 women exposed and 250 unexposed	Blood samples to analyze: FSH, LH, E2, PRL and PROG; Urine samples for BPA measurement	Evidence of disruptive activity of BPA on women's hormone homeostasis were found	MIAO, Maohua *et al.* (2015)[65]
Evaluate serum levels of BPA in exposed women with PCOS and hormonal and metabolic effects	62 women with PCOS and 62 healthy women	Serum samples to analyze BPA; Fasting blood; Triglyceride; Cholesterol HDL and LDL; TSH concentration and LH:FSH ratio	BPA levels were higher in BPA exposed PCOS women than the group of healthy women. Major differences in the other metabolic parameters	VAHEDI, Mahjoob *et al.*(2016)[66]
Search the presence of eight phthalate metabolites on women attending an infertility clinic and its possible correlations	112 women	Urine samples per cycle to measure 11 urinary phthalate metabolites	DEHP and DiDP concentrations were inversely associated with oocyte yield and number of matured oocytes at retrieval; DiNP and DiDP were associated with reduced fertilization; DEHP metabolites were negatively associated with probable clinical pregnancy and live birth following IVF	HAUSER, Russ *et al.* (2016)[67]
Study the concentrations of 8 phthalate metabolites	112 women attending an infertility clinic	Follicular fluid and urine samples	Most of the studied phthalates were highly detected in the ovarian follicular fluid of women undergoing IVF despite in lower doses than those shown to induce ovarian toxicity in animal studies	DU, Yao Yao *et al.* (2016)[68]

Note: BPA: Bisfenol A; PCOS: Polycystic ovary syndrome; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: 17β-Estradiol; PRL: Prolactin; PROG: Progesterone; TSH: Thyroid stimulating hormone; DEHP: Di(2-ethylhexyl) phthalate; DiDP: Di-isodecyl phthalate; DiNP: Di-isononyl phthalate; IVF: *in vitro* fertilization.

As can be seen in Table 5, a study in China found strong evidence that BPA is also disruptive to women's hormone homeostasis, compromising reproductive health. This cross-sectional study was based on the assumption that women working in a factory of epoxy resins, which is a major source of this dangerous chemical, would be much more exposed. As expected, the group of women working in the epoxy resin factory, had significantly higher serum levels of

bisphenol A than the group of workers in other factories. This study underlines the importance of assessing BPA contamination and all its concerns related to Human Health.[65]

The hypothalamic-pituitary-ovarian (HPO) axis is a complex system responsible for many processes, that must be functioning correctly in order to accomplish reproduction. If these complex interactions between the brain and the reproductive tract are disrupted, this system may alter its normal function, and lead to reproductive health problems, such as reduced fertility or even infertility itself.[79]

A study, performed on female rats, showed that early exposure to small doses of BPA has a huge impact on the normal function of the reproductive axis, where there are significant changes in the hormones.[70]

To investigate the effects of oral exposure to BPA on ovarian folliculogenesis and steroidogenesis, a study was conducted on adult female rats, which were exposed to different doses of environmental estrogen (BPA50 and BPA0.5). Ovaries from both BPA-treated groups showed some changes, corpora lutea numbers were increased with incomplete folliculogenesis. BPA50 group showed a reduced expression of androgen receptors at distinct stages. BPA0.5 showed a changed expression of AR where the expression of the mRNA-follicle-stimulating hormone receptor was higher. These results came to support the idea that folliculogenesis and steroidogenesis are targets of BPA.[69]

An additional study investigated the outcomes of BPA on female germline stem cells (FGSCs) and the development of mice ovaries. Female mice were administered solutions of BPA (12.5, 25 and 50 mg/kg/day). There was a slight increase in the number of follicles that had degenerated before coming to maturity, the atretic follicles. Furthermore, a reduction in the counting of primordial and primary follicles and corpus luteum was registered on higher concentrations of BPA. Another conclusion that came with this study was the suggestion that this chemical can accelerate ovaries apoptosis and promote the inhibition of its follicles.[73]

Speculations on the influence that the exposure of high concentrations of BPA has on the normal development of the ovarian follicles were the starting point for this study. Pre-puberty female rats were exposed to BPA (0 mg/kg, 10 mg/kg, 40 mg/kg, 160 mg/kg) to investigate its effects on ovarian development, and also the levels of expression on the development-related genes. In summary, BPA exposure during this pre-puberty period may interfere with the development and function of ovaries, and gene-related processes can be behind this mechanism of BPA toxicity during the development of the ovaries.[71]

The industry, when confronted with all the objections created against the use of BPA, started to use other compounds to replace it. Bisphenol S (BPS), bisphenol F (BPF), and bisphenol E (BPE) are three examples of BPA analogs, created to be inserted in the production of polycarbonates and epoxy resins. There are few studies about their endocrine activity and adverse health effects, but they raise similar concerns to BPA.[71] An example, is this study performed on CD-1 mice orally exposed to different concentrations of the analogs: BPA, BPE, or BPS (0.5, 20, and 50 μg/kg/day). The beginning of puberty and irregular estrous cyclicity, particularly with lower doses, was correlated to this exposure, as well as matting problems beginning at 6 months of age. By the time of 9 months, the pregnancy rate was diminished, and some deaths at birth were reported. All of this data conducts us to the dangerousness of the analogs and BPA itself, on fertility problems that can be observed later in life.[72]

Another class of plasticizers, which has been raising some concern related to the impact on female reproductive health, are phthalates. However, when compared to BPA is an impact much less studied.[80] The effects of phthalates on female reproductive health have been studied and highlighted by various in *vivo*/*in vitro* studies and some clinical trials too.

In this study, different doses of a mixture of three phthalates, DEHP, di-n-butyl phthalate (DBP), and benzyl butyl phthalate and two alkylphenols (1 and 10 mg/kg body weight) were administrated on female mice. This complex EDs mix was proven to modify reproductive parameters, such as the weight of the uterus and ovaries, the estrous cyclicity, levels on the reproductive hormones, and altered some features in the steroidogenesis too.[74]

Another research focused on the disruptive activity of another phthalate, DBP, analyzed the effects of a short exposure (10 days) in CD-1 mice. DBP showed evidence of ovarian toxicity, where alterations on different levels of hormones, such as luteinizing hormone (LH) follicle-stimulating hormone (FSH) and estradiol (E2) were verified. Complex processes as steroidogenesis were altered by the disruption of genes involved. Future work on clarification of how this endocrine disruptor may act on the changes at the gene expression is needed.[75]

DEHP is the most ubiquitous phthalate in the environment. There are already many studies about is disrupting activity in the reproductive female system. Lu *et al*., (2019)[76] evaluated complex factors, after administration during 14 days of 40 μg/kg body weight. This exposure resulted in expression problems, represented in Figure 3, in actin and Juno protein, the morphology of the spindle meiotic altered, also resulted in oxidative stress and apoptosis, the ATP content and mitochondria were also affected, DNA destruction, and epigenetic modifications in DEHP-exposed mouse oocytes.

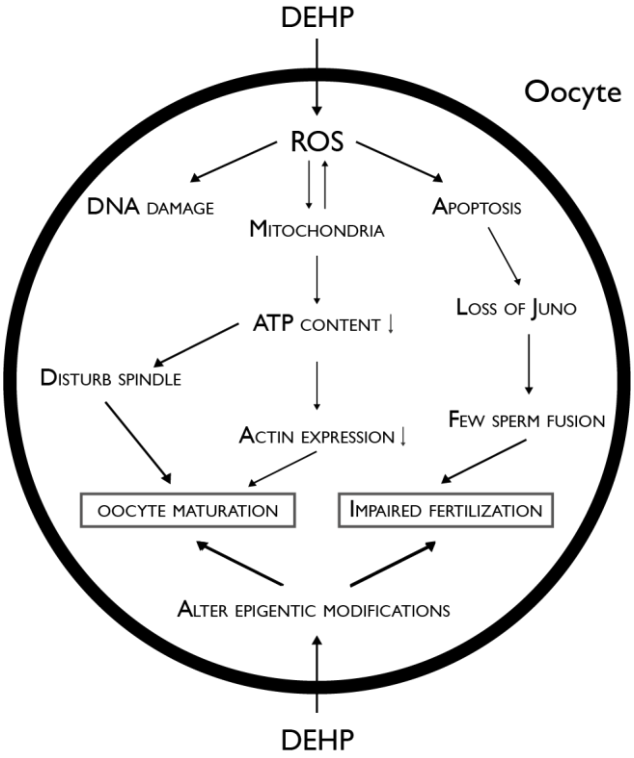


Figure 4: Comprehensive explanation about the possible mechanisms of action of DEHP (Adapted from LU, Zhenzhen *et al.*[76]). DEHP: Bis(2-ethylhexyl) Phthalate.

The results obtained confirm the disruptive activity that DEHP can cause on these structures, leading to the conclusion that this compound can diminish maturation and fertilization on oocytes. Disturbances in numerous processes as steroidogenesis that affect the hypothalamic-pituitary-ovarian axis formation were also found after the exposure in the mouse ovary.[81]

A prospective cohort study carried out between 2004-2012 analyzed two urine samples per cycle before oocyte retrieval from 256 women. Eleven phthalate metabolites (MEHP, MEHHP, MEOHP, MECPP, MiBP, MBP, MBzP, MEP, MCOP, MCNP, and MCPP) were measured. These urinary samples were evaluated in different models and women with the higher DEHP metabolites were directly associated with diminished oocyte production, clinical pregnancy, and live birth.[67]

Together, these data raise concerns about the impacts of plasticizers on female reproductive health. There is still a data gap that needs to be filled with more studies on this field, epidemiological studies, *in vivo* and *in vitro* studies, and environmental studies to clarify all the exposure routes to human health. Nonetheless is evident the association between this

class of chemicals environmental disruptors and female infertility, and the need for public awareness on this subject is urgent as well as the right protection against it.

4.2 Pesticides: Organochlorine and organophosphate compounds

The use of pesticides has been growing as mentioned above. The purpose was to improve agriculture, but not only affected the crop but also altered the food chain and the ecosystem. OCPs are a group of chlorinated compounds, widely used as pesticides, and known for their high persistence in the environment. Dietary exposure to OCPs and their damages to reproductive health is now the highlights of the research. They can be found among food items, fatty food and dairy products. [48,82]

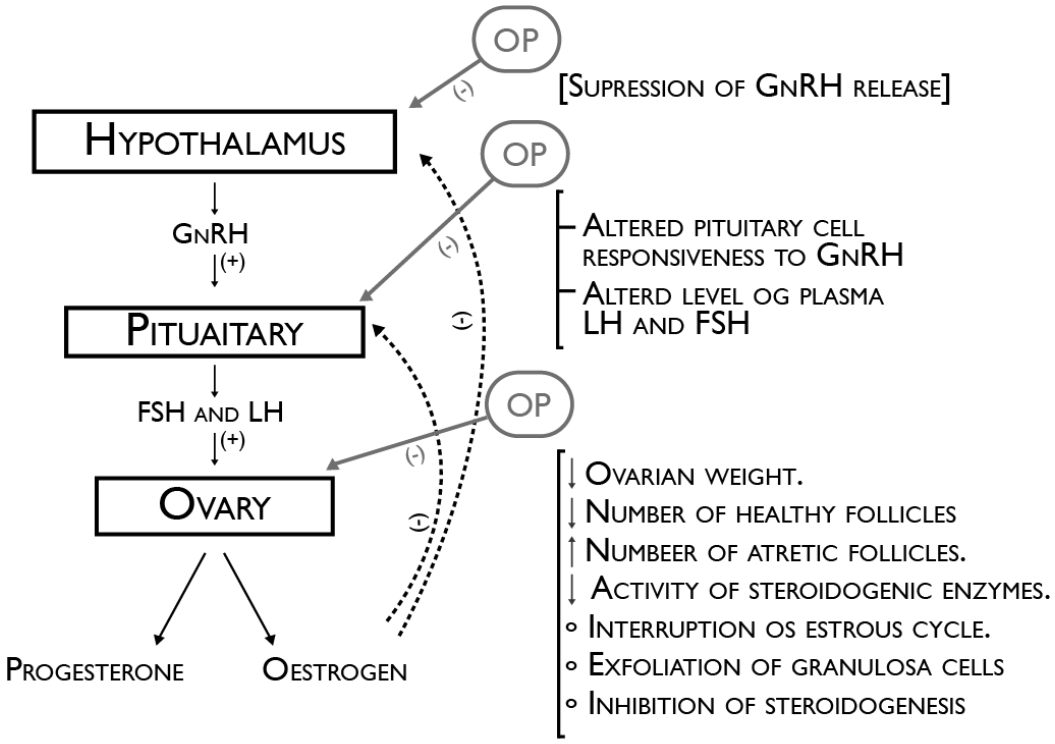


Figure 5: Schematic explanation of the OP potential target sites of action in the regulation of reproductive female functions through the HPG axis. (Adapted from Sikka *et al.*[29])

Another group of pesticides called organophosphate pesticides (OPs) has replaced some groups of organochlorines due to its fast degradation, a lower accumulative potential in the environment and animal tissues, a diminished possibility to enter to the ecosystem through food, and a greater selective process on causing toxicity only among insects and not on other vertebrates. However, studies present in Tables 6 and 7 reported their severe toxicity, and pointed out some OPS as probable disruptors on the reproduction physiology, even at very low doses. Impaired functions as processes of HPG axis are the result suspected by the release

of neurotransmitters by this class of pesticides, being this the mechanisms by which OPs interfere with the reproductive health system.[29]

Table 6: Observational studies of pesticides found in food.

Participants/subjects and research design	Patients	Patient parameters	Outcomes/Main conclusion of the study	References
Examine breast milk OCPs and their associations with female reproductive function	68 women	Breast milk	Dietary habit is an important factor influencing the levels of OCPs in breast milk and the associated risks for women	CHEN, Men Wen *et al.* (2018)[83]
Examine the association of preconception intake of pesticide residues in FVs with outcomes of infertility treatment with ART	325 women	FVs items in the FFQ and PDP, and Corresponding Scores for First, Second, and Third Measure, and PRBS	Higher consumption of high–pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART	CHIU, Yu Han *et al.* (2017)[84]
To see if there is an association of serum levels of typical organic pollutants with PCOS	50 women with PCOS and 30 normal controls	Serum levels	The PCOS group showed higher serum levels of PCBs, PAHs, and pesticides than the control group.	YANG, Qiaoyun *et al.* (2015)[85]

Note: OCPs: Organochlorine pesticides; FVs: Fruits and vegetables; ART: Assisted reproductive technologies; FFQ: Food Frequency Questionnaire; PDP: Pesticide Data Program; PRBS: Pesticide Residue Burden Score; PCOS: Polycystic ovary syndrome; PCBs: Polychlorinated biphenyls; PAHS: Polycyclic aromatic hydrocarbons.

Table 7: *In vivo* study with diazinon

Research design	Dosage regimen	Parameters monitored	Outcomes/Main conclusion of the study	References
To evaluate DZN effects on apoptosis of ovarian follicles in adult rats and also to assess the protective role of vit. E	Experimental group 1 (DZN+olive oil, 60 mg/kg), experimental group 2 (vit E, 200 mg/kg), and experimental group 3 (DZN+vit E, the same dosage)	Measure apoptosis of ovarian follicles	The number of apoptotic cells in experimental group 1 increased significantly in the contrast control group in secondary and graafian follicles. Administration vit E plus DZN, significantly reduced apoptotic cells compared to DZN group	SARGAZI, Zinat *et al.* (2015)[86]

Note: DZN: Diazinon.

In Taiwan, a study was conducted to examine OCPS in breast milk, and their association with female reproductive function, making connections with other parameters such as dietary and sociodemographic factors. 68 samples of breast milk were examined, and DDT and Hexachlorocyclohexane were the most abundant OCPs. Also, the relation between the presence of OCP residues in the breast milk and factor such as family income, cow milk, and beef intakes were positive. This study allows concluding about the tight connection between dietary habits and the exposure levels of OCPs.[83]

With the aim of investigating the possible outcomes of infertility treatment, when associated with the intake of pesticides present in fruits and vegetables, a study was conducted in a group of 325 women, under 541 assisted reproductive technologies at a fertility center. The exposure regime was divided into two groups of high and low exposure to pesticide residues present in fruits and vegetables, based on questionnaires performed on the woman involved. With this, it was possible to associate the consumption of higher levels of pesticides

with lower probabilities of achieving clinical pregnancy and live birth. On the other hand, no significant relations between low pesticide residues were made. This data suggest that dietary pesticide exposure, in a range of typical daily consumption, may be associated with adverse reproductive consequences.[84]

A preliminary case-control study undertaken at a reproductive Center with 50 women affected by PCOS, was taken upon the question if there is an association between this clinical condition and serum levels of organic pollutants. The results of this study take us to the positive relation between PCOS and organic pollutants, since the serum levels were substantially higher in PCOS group when compared to the control one, especially DDE and polychlorinated biphenyls (PCBs).[85]

DZN is another concerning organophosphate insecticide extensively used in agriculture that is responsible for many negative effects on humans, including reproductive ones. This study evaluated the effects of DZN on apoptosis of ovarian follicles in adult rats and also assessed the possible protective role of vitamin E. Thirty adult female rats were divided into groups, control, sham, and two experimental (one with DZN+olive oil, another with only vit.E and DZN+vit.E). As expected, DZN demonstrated apoptotic activity in secondary follicles (group with DZN+olive oil), and another interesting data was that the group DZN+vit.E exhibited a protective role on DZN toxicity.[86] This compound is also pointed as an inducer of oxidative stress, in tissues such as the reproductive system. Other studies had already approached the protective role that this vitamin can display, showing some interesting data on this concern.[87]

The interest within the general population on this matter has been rising in the last decades. A growing concern in the search for organic products, free from pesticides, antibiotics, and genetically modified organisms has been observed. In general terms, the awareness on this topic has been growing, and in this line a more conscious attitude about environmental contamination which leads to a higher demand for organic products[88,89]

There are already many different studies on the benefits of the consumption and preference for organic food, as well studies that compare the exposure of pesticides, through the analyses of the urine, that confirms the positive relationship between consumption of organic food and lower pesticides metabolites in the urine.[90,91]

4.3 Dioxins and Dioxin-like compounds

Major concern over the chemical group of dioxins has arisen since the discovery of the highly toxic and teratogenic TCDD. They belong to the persistent organic pollutants and act via a common mechanism that consists of stimulating the receptor of aryl hydrocarbon. The main source of dioxins in animals and humans is through food, and due to their highly lipophilic profile, they tend to accumulate in tissues with a high-fat percentage. The metabolism and excretion of these chemicals are generally extremely slow.[92,93]

Table 8: Observational studies with dioxins found in food.

Participants/subjects and research design	Patients	Patient parameters	Outcomes/Main conclusion of the study	References
Examined relationships of TCDD exposure with TTP (TTP, the monthly probability of conception within the first 12 months of trying) and infertility (12 months of trying to conceive)	981 women exposed to TCDD in a 1976 accident	Serum TCDD concentration and estimated TCDD concentration at pregnancy	TCDD exposure may be associated with decreased fertility in Seveso mothers and potentially in their daughters exposed in utero	B. ESKENAZI, J. AMES,S. RAUCH *et al.* (2020)[94]
To study the levels of biologically active dioxin-like substances in adipose tissue of patients with DIE	30 patients	Dioxin-like substances were analyzed in adipose tissue	The total toxic equivalence and concentrations of both dioxins and PCBs were significantly higher in patients with DIE	MARTÍNEZ-ZAMORA, M. A. *et al.* (2015)[45]

Note: TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; TTP: Time to pregnancy; DIE: deep infiltrating endometriosis; PCBs: Polychlorinated biphenyls.

Table 9: *In vivo* studies with dioxins found in food.

Research design	Dosage regimen	Parameters monitored	Outcomes/Main conclusion of the study	References
To investigate the effect of maternal exposure to TCDD on ovaries	TCDD (100 ng/kg or 500 ng/kg) or only vehicle and corn oil	The vaginal opening and estrous cycle of female offspring rats were monitored twice a day. The ovarian histology, follicle counts, real-time PCR, western blotting, and DNA methylation analysis about Gdf9 and Bmp15 were carried out in F1 rats	Maternal exposure to TCDD could affect the ovary development and functions which were possibly associated with down-regulation of mRNA and protein expression of GDF9 and BMP15	ZHANG, Xiuli *et al.* (2018)[95]
The aim of our study was to evaluate the effect of ancestral TCDD exposure on ovarian toxicity in offspring rats (F3), focusing on the Igf2/H19 pathway	100or 500 ng/kg BW/day	Ovary coefficient; Vaginal opening time; Regularity of estrous cycle; Ovarian pathology; Follicles counts; Apoptosis of granular cells; Levels of E2, FSH, and LH	Our data showed that ancestral TCDD exposure may impair transgenerational adult ovary development and functions	YU, Kailun *et al.* (2019)[96]

Note: TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; PCR: Polymerase chain reaction; BW: Bodyweight; E2: 17β-Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

Some studies (Table 8) have investigated the correlation between the serum levels of dioxin-like substances in patients with endometriosis. Endometriosis is an estrogen-dependent disease of the reproductive feminine health tract. [52,97] Adipose tissue from patients diagnosed with endometriosis was analyzed and compared to a control group, to see if there was a

positive correlation with the presence of dioxin-like substances. Their results suggest a relation between this exposure and this female disorder.[45,47]

Since Seveso's incident in 1976, a huge study called Seveso Women's Health Study (SWHS) was created to follow 981 women that were exposed to TCDD. In the last report of this study population, the median factor time to pregnancy (TTP) on SWHS women was 3 months, but 18% reported TTP≥12 months. On other hand, SWHS daughters had different results, their median TTP was 2 months, and 11% reported taking more than 12 months to conceive. The results expressed an association between TCDD exposure and decreased fertility and probably exposure *in utero*.[94]

To investigate the effect of TCDD exposure on maternal ovaries, a study summarized in Table 9 was performed on pregnant rats treated with TCDD with different doses (100 and 500 ng/kg), contrasting with a control group (corn oil). Ovary weight, E2 and FSH concentrations, estrous cycles, and the number of follicles were studied factors that expressed changes. The results obtained in this study demonstrated that the exposure in utero of TCDD, especially the highest exposure level, may display a significant change in the parameters evaluated, leading us to its possible negative role on the ovary development and its functions. It was also made a positive relation between the down-regulation of mRNA and protein expression with these outcomes.[95]

On the same matter, but studying the transgenerational impact on F3, another study assessed the TCDD exposure and ancestral effects on ovarian toxicity, directing their attention to the Igf2/H19 pathway, an important route for follicular development. F0 pregnant rats were divided, and some received the TCDD in 100 or 500 ng/kg BW/day and others vehicle as part of the control, through 8-14 days of gestation. The results indicated a decrease in the ovarian coefficient, LH concentration, number of primary follicles, and a rise in the apoptosis of granular cells was also registered. Through an RT-PCR analysis, it was possible to record an increased level of expression on H19 mRNA in ovaries treated with F3. All this data led us to the transgenerational impairment on the adult ovary enhancement and functions when exposed to TCDD and possibly bound to an Igf2/H19 inhibition.[96]

Equine gametes were also investigated to study the effect of TCDD exposure (0.32 ng, 3.2 ng, and 32 ng/mL). 28.38% of the oocytes under the lowest concentration reached the oocyte maturation and on the 3.2 ng/mL the percentage was reduced to 5.14%. The highest concentration in the study was 32ng and non-matured oocytes were observed. This came to add evidence of the negative impact on the female reproductive system.[98]

The awareness on this matter is urgent. There is still a lot to study and ascertain about the effects on reproductive health coming from dioxin exposure. It is clear that there are intrinsic harmful effects, but the mechanism behind it and all the physiological processes within are still very unclear. There are a lot more studies connecting this chemical family with male reproductive health when compared to females, and even with a lot more biography uncertainties still exist.

5. Conclusion

In the last two decades, there has been a growing awareness of endocrine-disrupting chemicals and their possible adverse effects on human health. This subject is considered a severe health problem worldwide, as well as infertility. Data from WHO revealed that nowadays about 48 million couples and 186 million individuals suffer from infertility around the globe. Where these two subjects meet is determined by the intimate role that these endocrine disruptive chemicals play in female and male infertility, being the female infertility the focus of this study.[1]

During the past 6 years, several studies examined the effects of endocrine disrupting chemicals on female fertility. Collectively, these studies showed that the compounds that are most frequently related and responsible for regarding female fertility are plasticizers, particularly BPA and phthalates, such as DEHP and its metabolites, organochlorine, and organophosphate compounds, namely diazinon, and dioxins and dioxin-like compounds.

The first two groups interfere with different processes within ovarian development, such as folliculogenesis, steroidogenesis, development of the female germline stem cells, follicle formation, and also present strong associations with diseases such as PCOS. The imbalance of the HPO axis is another issue pointed out for the failure of the reproductive tract, generating disturbances in hormone homeostasis.

Organochlorine and organophosphate compounds have also been shown to affect ovaries parameters as well as the mentioned above. They have been proven to induce follicles apoptosis and display impaired processes on the HPO axis. Associations between this family of chemicals and ovaries diseases, such as PCOS, were also established.

At last, dioxins and dioxin-like compounds are also related to female infertility, however, there is a lot to explore in this group, especially related to female health issues. The most presented compound throughout the research was TCDD, which was shown to have a clear negative impact on the female reproductive tract, displaying threats to ovarian function and other related diseases for example endometrioses. The TTP was also reduced when exposed to this chemical, which is another indicator of the negative role of the biological processes regarding reproduction.

The endocrine system is complex, which consists of one difficult barrier on the discovery of the different mechanisms around these compounds. Whereas this exposure can trigger failures on the reproductive system or not, has created a credible and alarming question. The

biological complexity behind it is still to discover and clarify. The present literature review revealed that despite all the quality work involving all the scientific community, a lot more is needed to solve this complex and urgent subject that created a major threat to Human Health. In this line, large, double-blind, placebo-controlled randomized clinical trials are needed to better understand the mechanisms of action of these compounds in female infertility, as well as the doses and frequency of exposure responsible for it. It would also be of great value to know which compounds (e.g. vitamins) can play a protective effect regarding the Human Health damages caused by endocrine disruptors.

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